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THE CARRIER PROBLEM IN INFECTIOUS DISEASES

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THE CARRIER PROBLEM IN INFECTIOUS DISEASES

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GENERAL EDITORS' PREFACE

THE Editors hope to issue in this series of International Medical Monographs contributions to the domain of the Medical Sciences on subjects of immediate interest, made by first-hand authorities who have been engaged in extending the confines of knowledge. Readers who seek to follow the rapid progress made in some new phase of investigation will find herein accurate information acquired from the consultation of the leading authorities of Europe and America, and illuminated by the researches and considered opinions of the authors.

Amidst the press and rush of modern research, and the multitude of papers published in many tongues, it is necessary to find men of proved merit and ripe experience, who will winnow the wheat from the chaff, and give us the present knowledge of their own subjects in a duly balanced, concise, and accurate form.

Drs. Ledingham and Arkwright in this volume deal with a subject of the greatest importance to public health. They have made an elaborate study of the doctrine that diseases, like typhoid fever, cerebrospinal fever, diphtheria, cholera, and dysentery, are propagated through the agency of human "carriers"—*i.e.*, individuals outwardly healthy, or at most suffering from some trivial chronic complaint. The discovery of "carriers" has opened out a new department of hygiene, and the question of legislative control of such has become a matter of immediate practical importance. Up to date no such exhaustive treatise on the "carrier" problem as that of Drs. Ledingham and Arkwright has been published.

LEONARD HILL.
WILLIAM BULLOCH.

October, 1912.

AUTHORS' PREFACE

Our object in writing the following pages has been to present, in as complete a form as possible, the present state of knowledge with regard to the rôle played by the human carrier in infectious diseases. It is needless to urge at the present time the importance of carriers, since it is widely recognized that they indicate one of the most promising lines along which epidemiology is advancing.

At first sight it may appear arbitrary to have selected six diseases, and to have confined our attention solely to them. It is, however, only in these instances that sufficient exact knowledge is at hand on which to base a statement as to the importance of carriers. There is little doubt that before long it will be possible to include a considerable number of other infectious diseases in the same category. In the meanwhile these six diseases may serve as the examples for which the facts have been most accurately, if incompletely, worked out. In compiling the book we have had the benefit of personal experience, and also of the work of our colleagues, especially in connection with typhoid fever, diphtheria, cerebrospinal meningitis, and dysentery. Though approaching the subject mainly from the bacteriological side, we have tried to correctly appreciate the epidemiological point of view, and to correlate the work done in the two departments. We hope that the book may prove to be of service, not only to epidemiologists and public health authorities, but also to bacteriologists who may have to undertake work in connection with carriers.

J. C. G. LEDINGHAM.
J. A. ARKWRIGHT.

October, 1912.

CONTENTS

CHAPTER I

PAGE
INTRODUCTORY - - - - - - - - 1

CHAPTER II

THE CARRIER PROBLEM IN ENTERIC FEVER - - - 5

CHAPTER III

PARATYPHOID FEVER, AND THE INFECTIONS CAUSED BY ORGANISMS OF THE GAERTNER-PARATYPHOID GROUP - - - 136

CHAPTER IV

DIPHTHERIA - - - - - - - - 163

CHAPTER V

EPIDEMIC CEREBROSPINAL MENINGITIS - - - - 227

CHAPTER VI

DYSENTERY - - - - - - - - 270

CHAPTER VII

CHOLERA - - - - - - - - 295

INDEX 313

THE CARRIER PROBLEM IN INFECTIOUS DISEASES

CHAPTER I

INTRODUCTORY

The part played by human carriers in the spread of infectious disease is on all sides gaining wider recognition, and the problem of dealing effectively with these sources of infection has become one of prime importance to the administrator of public health. It is primarily to the labours of the bacteriologist that our present knowledge of the carrier status is due ; and although on the epidemiological side a few dissentient voices have been raised in protest against the attachment of undue importance to the human carrier, the great majority of public health administrators have welcomed the new knowledge, and are eagerly calling on the bacteriologists to give them a further lead. It is recognized that a human carrier who has been proved to be a source of infection cannot be dealt with in the same drastic fashion as an inanimate and probably innocent fomes, and accordingly the services of the bacteriologist and experimental pathologist are being requisitioned to find a way out of this new impasse.

In the following pages our object has been to present the facts on which is based the view that the carrier plays such a pre-eminent part, not only in furthering the spread of an epidemic already arisen, but in conserving the seed of further epidemics. Hitherto precise knowledge of the influence of the human carrier is available only in the case of the infectious diseases studied in these pages, but evidence is already accumulating which at least suggests that in other epidemic diseases—for example, in acute anterior poliomyelitis—the human carrier may act as a focus of infection. For reasons of space it has been impossible to extend the scope of this book to include the discussion of the rôle of animal carriers—*e.g.*, of goat-carriers in the case of Malta fever, and of insect-carriers generally in the case of protozoan infections. Of the epidemic diseases treated in this book, enteric fever, diphtheria, and, to a lesser extent, cerebrospinal meningitis, are of prime concern to the public health administrators in this country; but it is hoped that the evidence put forward with regard to cholera and bacillary dysentery may prove of value to practitioners and health experts abroad. For the sections on Diphtheria, Dysentery, and Cholera, one of us (Dr. Arkwright) is responsible; while the other (Dr. Ledingham) has undertaken those on Enteric Fever, Paratyphoid Fever, and Cerebrospinal Meningitis. With regard to the section on Enteric Fever, this has to a very large extent been reproduced from the writer's report on the subject to the Local Government Board, which appeared about eighteen months ago. Many of the less essential details and illustrative examples of carrier infectivity recorded in that report have, however, been omitted, but, on the other hand, full reference has been made to all important papers which have appeared in the short interval.

The study of the carrier problem, particularly from the bacteriological point of view, has necessitated considerable modification of our conception of the nature of infection. Bacteriological research in the course of recent epidemics of enteric fever, diphtheria, cerebrospinal fever, and cholera, has revealed the fact that the clinical manifestation of an infection may vary from the typical description of the textbook to the very minimal dimensions which, possibly, only serological analysis can detect. In typhoid fever, for example, two fairly distinct types of carrier have been shown to be potent in the spread of infection—viz., the transitory carrier whose infection has probably been so slight as to be completely overlooked, and the chronic carrier whose infectivity in domestic, institutional, and milk-borne outbreaks has time and again been proved beyond question. It is the chronic carrier who forms the first link in a chain of cases constituting a fresh outbreak, while the transitory carrier whose infection has been abortive, and the precocious carrier whose symptoms have not yet set in, are very potent factors in the further spread.

In the interests of preventive medicine, the chronic carrier has the first claim on our attention, as it is he who is immediately responsible for the recrudescence of infection, whether in endemic or explosive form.

The invocation of a prolonged sojourn of specific micro-organisms in inanimate nature can no longer be considered valid, although no one would question the fact that inanimate objects may frequently play the part of intermediaries. The thesis of Pettenkofer, that the soil acts as a medium in which the specific micro-organisms of cholera and enteric fever pass through a ripening process requisite for their further ability to infect, has now been almost entirely abandoned, nor has any constant relationship been found between the typhoid frequency and the ground-water level. As permanent sources of infection we are left with the human carrier, and if we succeed in curing this person or in preventing the acute infection from culminating in the carrier state, there is every hope that diseases such as typhoid fever may become extinct. It is probable that the term "healthy" as applied to the chronic typhoid carrier, may have to be abondoned in favour of the term "chronic typhoid infection," in view of the fact that gall-bladder troubles are liable at any moment to supervene. Cases of recurring gall-stone colic in chronic typhoid carriers are notorious, and although the enjoyment of health in the interval may be normal, such a person must certainly be considered as living on the brink of a volcano. He is, in fact, suffering from a latent infection which happens to be not incompatible with the enjoyment of fair health. To the chronic typhoid urinary carrier the term "healthy" can probably in rare cases only be applied. Such cases have been shown to be suffering from a genuine chronic typhoidal infection of the genito-urinary system, which is inconsistent with general well-being, and there is no doubt that such cases, fortunately rare, should be made the subject of extensive clinical and surgical research.

The foregoing considerations apply not only to typhoidal and paratyphoidal infections, but also in varying degrees to all those diseases which depend largely for their perpetuation and transmission on the existence of carriers. Like typhoid carriers, diphtheria carriers may be apparently in perfect health, but more frequently the persistence of the bacillus is associated with unhealthy local conditions, especially when the infection is of sufficient duration to merit the term "chronic."

Dysentery carriers, again, are frequently liable to recurrent mild attacks of diarrhœa, doubtless due to the lodgement of the bacilli in the intestinal wall.

Similar considerations appear to hold for the various grades of disease carriers. The greater the intimacy with which the disease germ is associated with the tissues of the carrier, the more likely it is that the said germ will remain as a truly chronic inhabitant.

The proposition may not be invariably true, but a moment's consideration will suggest, on the one hand, instances in which a passive and probably temporary human carrier is responsible for conveying infection in such diseases as puerperal fever, where the infecting streptococcus as a rule causes no lesion in the carrier; and, on the other hand, instances of a truly chronic disease, such as leprosy or tuberculosis, in which the carrier is unhesitatingly pronounced to be diseased, but is frequently unisolated, and consequently may distribute untold millions of bacilli from a chronic ulcer or pulmonary cavity.

Between these two classes of purely passive and truly healthy carriers on the one side, and undoubtedly diseased chronic cases which act as carriers on the other side, come the class of carriers specially dealt with in this volume.

These latter are as a rule either in fair health or not obviously diseased. There is especial need, therefore, that attention should be directed to them, and that their importance should be proclaimed with unremitting insistence, because these carriers are not sufficiently unwell to be restricted in their habits and occupations, and are apt to pass unheeded unless subjected to bacteriological investigation.

CHAPTER II

THE CARRIER PROBLEM IN ENTERIC FEVER

I. INTRODUCTORY.

HISTORICALLY the conception of the typhoid carrier state, in so far as its epidemiological bearings are concerned, was directly evolved from the views set forth by Robert Koch in his famous address of November, 1902, which had as its main outcome the setting in motion of an elaborate machinery for the scientific investigation of the rise and spread of enteric fever.

The influence of this address on the epidemiology of infectious diseases generally it would be difficult to over-estimate.

Koch's main thesis was that the typhoid patient or the typhoid convalescent who happened to harbour the specific germs was the most fruitful source of further infection. He therefore laid particular stress on the necessity of rendering the typhoid patient innocuous to those in contact with him—by efficient disinfection of the excreta, both during the disease and in convalescence, by careful inquiry into, and supervision of, the ambulant and abortive cases, and especially of those anomalous types met with so frequently in children.

At Koch's recommendation bacteriological stations were instituted in the typhoid-ridden districts, notably in South-West Germany, for the purpose of testing in actual practice the validity of his dictum, that the chief source of typhoid infection is to be found in man himself. These institutes have proved fruitful not only in helping to check the further spread of epidemics already arisen, but also in explaining the causation of many epidemics the source of which could not be traced to contact with the typhoid patient, or to other commonly recognized agencies of infection; in fact, the discovery of the typhoid carrier was a natural sequence of the systematic bacteriological examination of the typhoid convalescent. That persons apparently quite healthy could harbour typhoid bacilli after an attack of the fever, emit them continuously or periodically in the excreta, and thus act as potential sources of infection, was a new fact in the etiology of enteric fever. It had certainly been demonstrated several years previously that the typhoid bacillus might remain for long periods in the gall-bladder, bone abscesses and other situations, but the exact significance of such finds from the epidemiological point of view had not been thoroughly realized. Such findings, so far as they concern us here, will be dealt with in a later chapter on the pathogenesis of the carrier state. The carrier of prime importance is the person who excretes the specific germs continuously or intermittently in the fæces or urine, and it is to this person that our attention will be mainly devoted in these chapters.

As much of the earlier knowledge of the typhoid carrier question has emanated from the bacteriological stations in South-West Germany, it may be well here to refer briefly to their constitution and scope of work.

In thus giving prominence to the efforts of the hygienists and bacteriologists in the South-West Germany campaign, I do not wish it to be implied that the discovery of the carrier condition was entirely a German product, or even that the epidemiological importance of the carrier was first grasped by the Koch school. The intestinal carrier—the most important because the most frequent type—undoubtedly came to light as the result of the German campaign work; but the chronic urinary carrier—the much rarer, though probably more dangerous, type—was known at least three to four years before Koch's famous address in November, 1902, and in this country Horton - Smith (1900) had already called attention to the etiological importance of the latter, in his Goulstonian Lectures in 1900. There can be no question, however, that it is to the concentrated efforts of the German typhoid campaigners that we owe the larger part of our material for this new chapter on the etiology of typhoid fever.

In the flat south-western portion of Germany, typhoid fever had become so prevalent, particularly in the Regierungsbezirk Trier, the Bavarian Pfalz, and in Alsace-Lorraine, that a general spread of the disease by the floating industrial population of this district to all parts of Germany began to be dreaded. On Koch's recommendation, an experimental typhoid station was planted at Trier in 1903, under the directorship of Frosch. Such excellent service was rendered by this station in elucidating the spread of enteric fever that it was determined to increase largely the number of such institutes where co-operative epidemiological and bacteriological work could be carried out. There were in existence and in full swing in the year 1907 eleven such stations, with a staff of thirty-five bacteriologists attached to them ; but in the course of the last two years a few of these special institutes have been disbanded.

It may not be amiss to explain briefly the main functions which these special stations subserve. Their chief task was the bacteriological examination of suspected material from patients, with a view to accurate diagnosis. The medical staff were empowered to prosecute their inquiries on the spot in conjunction with the official authorities. In searching out concealed cases, they had at their disposal the police notifications of strangers in the district, the school absentee lists, dispensary lists, the official death notifications, the lists of employees in manufactories, etc. Further, they were empowered to procure information from the clergy, the school teachers, and the midwives.

The aim of these inquiries was to search out as early as possible all typhoid cases and carriers, to explain the source of infection in each case, to take active measures against the existing focus of infection, and to prevent the further spread of the disease.

Undoubtedly the efficiency of these institutes lay in the fact that epidemiological and bacteriological inquiry went on simultaneously, to the great advantage of both. To the lay country people, also, the foundation of these institutes in their midst could not fail to appeal forcibly, and it is more than likely that the comparative ease with which samples of excreta and other material were obtained was in great measure due to this fact.

Lentz (1910), in a paper before the British Medical Association, gave a brief account of the great services rendered by the German campaigners in elucidating the spread of endemic typhoid fever in South-West Germany. He also referred to the great reduction in the incidence of typhoid fever in the campaign area since the commencement of operations.

II. GENERAL FACTS REGARDING TYPHOID CARRIERS; TYPES OF CARRIERS, CLASSIFICATION, AGE, SEX, FREQUENCY, ETC.

The earlier efforts of the typhoid institutes in South-West Germany contributed an enormous amount of information on the part played in the spread of typhoid fever by contact of the affected person with the healthy, and abundantly confirmed the views promulgated by Koch. An excellent account of the investigations at Trier during the earlier months of the campaign is given by Frosch (1903), and at Saarbrücken by Drigalski (1904). These investigations, together with those of Dönitz (1903) in Berlin, served to illustrate the significance of atypical enteric fever in children, and of the ambulant, abortive, or completely unrecognized types of the disease. Although, however, contact infection from the sick to the healthy was a powerful, if not the most powerful, factor in the spread of enteric fever, they found that there was a fairly large quota of recurrent outbreaks of typhoid fever, mostly confined to isolated houses or groups of houses in country districts or streets, where no such contact with an obviously sick person could be traced. This circumstance, together with the knowledge acquired many years before, that the typhoid bacillus might in certain cases remain for long periods in the body in association with bone abscesses, cholelithiasis, etc., led Frosch to put forward the suggestion that possibly in the intestinal tract also the infective germs might lead a saprophytic existence, and by their intermittent discharge into the outer world lead to further infection. Frosch's suggestion was a happy one, and has been entirely confirmed, not only by the subsequent investigations in South-West Germany, but in all countries where the subject has received attention.

To Drigalski (1903 and 1904) belongs the merit of establishing on a bacteriological basis the hypothesis put forward by Frosch, then Director of the Typhoid Commission, that the *Bacillus typhosus* might in certain cases lead a prolonged saprophytic existence in the human intestine. When he wrote the account of his experiences at Saarbrücken, this institute had been in existence only ten months. During that time he had been much impressed by the repeated occurrence of enteric fever in certain houses and in towns where the sanitary conditions appeared quite satisfactory. To explain this phenomenon he had to assume the possibility of a prolonged existence of the typhoid bacillus outside the body, but this view he very soon abandoned in consequence of the bacteriological results he obtained in a series of typhoid cases. The stools in sixty-four cases of typhoid fever were examined bacteriologically at different times during the disease, and also during convalescence, with the following results:

Time.	Typhoid Bacilli Present.	Percentage.
1st to 5th day of the disease ..	10 cases	15·6
6th ,, 10th ,, ,, ...	15 ,,	23·4
11th ,, 20th ,, ,, ...	21 ,,	33·0
21st ,, 27th ,, ,, ...	8 ,,	11·5
After 8 to 10 weeks	7 ,,	11·0
After 3 months and later	3 ,,	4·7

The longest time during which the *B. typhosus* was demonstrable in the stools was fourteen weeks, and in a footnote, referring to a later date, he observes that in this particular case the bacilli were still present at the end of nine months, when they formed 50 to 60 per cent. of the total flora. This case would therefore constitute the first recorded chronic carrier traced from convalescence onwards.

To Drigalski also belongs the merit of having been the first to discover a female chronic carrier, who apparently gave no history of having passed through an attack of typhoid fever.

Some of these facts, which had been detailed a few months previously by Drigalski at a scientific meeting, together with certain parallel observations on convalescent urinary carriers made by Dönitz (1903) in Berlin, had afforded a reasonably strong foundation for the hypothesis formulated shortly afterwards by Frosch.

It will be appropriate at this point to refer briefly to the facts which have accumulated regarding the excretion of typhoid bacilli by the typhoid patient during the course of the disease. We shall then be in a position to appreciate the analogous statistics with regard to convalescents and carriers.

Excretion of Typhoid Bacilli by the Typhoid Patient.

In the first place, with regard to the fæces, it would now appear that the proportion of instances in which the typhoid bacillus may be detected in the fæces at one or another stage of the disease depends almost entirely on the degree of efficiency of the bacteriological methods in current use. We have already referred to the earlier data of Drigalski, whose highest percentage (viz., 33 per cent. in a series of 64 cases) was obtained during the third week of the disease, whereas in the first five days only 15·6 per cent. were positive. Much higher values than these have been recorded in recent years.

Brion and Kayser (1906) examined a series of 144 cases during the febrile period, with the following results :

	Cases examined.	Positive.	Per Cent.
1st week	22	7	32
2nd ,, ...	51	18	35
3rd ,, ...	71	31	45

Bohne (1908) examined twenty-seven cases, and obtained the highest percentage during the fourth week, but his series is too small for statistical purposes :

	Cases examined.	Positive.	Per Cent.
1st week	2	0	0
2nd ,, ...	13	3	23
3rd ,, ...	7	3	43
4th ,, ...	4	4	100
5th ,, ...	1	1	—

By the aid of the more recently introduced media, Gaehtgens and Brückner (1910) have obtained, in a series of seventy-two cases, the following results, which may be considered the best attainable at the present time :

	Cases examined.	Positive.	Per Cent.
1st week	21	12	57
2nd ,, ...	32	17	53
3rd ,, ...	13	10	77
4th ,, ...	4	2	50
5th ,, ...	2	2	—

To summarize, in about 75 to 80 per cent. of typhoid cases examined during the third week, typhoid bacilli are demonstrable in the fæces, and it is not unlikely that with further improvements in technique a still higher percentage will be obtained.

Excretion of the Specific Bacilli during the Incubation Stage.

G. Mayer (1910) in a recent paper states that in 1903 he was the first to demonstrate the presence of typhoid bacilli in the stools during the incubation stage. The case was a boy of six years, whose stools contained typhoid bacilli eight days before symptoms arose. Although he was immediately isolated, both his brothers contracted the fever. In 1905 and 1907 the same author was able to record two further cases of this nature.

Conradi (1907*b*) also gives notes of two cases in which the bacilli were found in the fæces during the incubation stage, and I shall have occasion to refer later to some statistics collected by Conradi bearing on this question.

With regard to the urine, the isolation of typhoid bacilli, if present in this fluid, is as a rule a simple matter. Most observers are agreed that in about 25 per cent. of all cases of typhoid fever it is possible to demonstrate the bacilli in the urine. They appear generally in the later stages of the disease, after defervescence (Herbert, 1904), or in late convalescence, but they have also been found frequently at the period of eruption of the rose spots. Further data on this subject will be found in the chapter on Urinary Carriers.

Statistics with Regard to the Excretion of Typhoid Bacilli during Convalescence.

On this question data collected by various individual observers are available, and it may here be remarked that it has been customary to take a period of ten weeks, dating from the commencement of the attack or a relapse, as the limit of what may be called the normal period of residence of *B. typhosus* in the organism which has survived the infection. Persons in whom the specific bacilli continue to vegetate beyond this period, but not longer than three months, dating from the commencement of the attack, have been assigned for convenience to the somewhat arbitrary category of "temporary" carriers (or Bazillenträger); while those who remain infected for any period beyond the three-month limit have been assigned to the category of "chronic" carriers (or Dauerträger). As we shall see later, it will prove more convenient to extend the three-month limit for the temporary carrier to one year, in view of the fact that a very large proportion of these persons who remain infected at the end of three months apparently get rid of the specific organisms by the end of one year. The terms "temporary" and "chronic" carrier are, however, sufficiently precise in the case of persons who have actually recovered from a definite attack of enteric fever, or from whom an unequivocal history of enteric fever can be elicited.

It is not possible, however, to obtain accurate data regarding the previous history of every person who is discovered to be a carrier. As we shall see later, a large proportion of these carriers have not been found to present a history of known typhoid infection. Others, again, are able to supply data which at least suggest that they may have previously suffered from some form of ambulant or abortive typhoid fever, while others have been traced to the chronic stage right from the primary infection.

Conradi (1907) adopted the classification of primary, secondary, and tertiary carriers. To the first group (primary) belong those carriers in whom the infection has not led to the occurrence of symptoms of enteric fever. In this group Conradi includes those cases in which the excretion of typhoid bacilli has been found to take place during the incubation stage.

To the second group (secondary carriers) belong those who, having been attacked by enteric fever, continue to pass the bacilli for some time beyond a period of ten weeks from the commencement of the attack.

To the third group (tertiary) belong those who continuously pass the bacilli after the primary attack.

This classification of Conradi's is not to be recommended, as the terms employed raise no clear idea in the mind as to the conditions they connote.

Sacquépée (1910) has recently suggested a more intelligible classification of carriers—thus:

GROUP I.: *Porteurs précoces* (precocious carriers)—*i.e.*, those who have taken the typhoid bacillus into the system, but who as yet do not present any symptoms of infection. This group would consist only of carriers in the incubation stage.

Group II.: Persons who have recovered from typhoid or some typhoid-like infection, but who continue to excrete the bacillus whether for a short or for an indefinite period.

Subgroup A.: Porteurs convalescents, in whom the excretion ceases before the end of the third month.

Subgroup B.: Porteurs chroniques, in whom the excretion lasts for an indefinite period.

Group III.: *Porteurs sains* or *porteurs paradoxaux*—*i.e.*, those who have never had symptoms of typhoid fever, but who may excrete the bacillus over an indefinite period.

It will be seen that the primary carriers of Conradi include both the precocious and the paradoxical carriers of Sacquépée.

There is no doubt that this classification by Sacquépée is a fairly comprehensive one, but a sharp line of demarcation cannot always be drawn between Group I. and Group III.; and probably many of the so-called "paradoxical" carriers would be found to fall into the category of the convalescent or chronic carriers, if sufficient details as to their previous history were available.

For ordinary descriptive purposes we shall find that the terms "temporary" (or transitory) and "chronic" carriers are sufficiently explicit to denote the two great groups with which we have to deal.

In the course of this survey it will be seen that very important differences exist between these two great groups of convalescent carriers.

Data of Lentz.—I now pass to the consideration of Lentz' (1905) results obtained in the course of his examination of typhoid convalescents, at his institute in Idar. Out of 400 convalescents, Lentz reported that six continued to excrete the bacillus for a longer period than ten weeks, dating from the beginning of the disease or from the beginning of a relapse. None of these six cases, however, continued to be infective for a longer period than thirteen months, when repeated examination showed that the excreta were typhoid-free. There was thus an apparent late cure in the bacteriological sense, but, as we shall subsequently show, such "cures" must be regarded with great caution.

Though these six persons ultimately became typhoid-free, twelve others did not rid themselves of the bacilli once they reached the chronic stage. The total percentage of carriers in

Lentz' series was therefore 4·5 (1·5 per cent. temporary carriers and 3 per cent. chronic carriers).

Out of 400 typhoid convalescents, Conradi got 22 secondary carriers (compare Lentz' figure of 1·5 per cent.) and 2 tertiary carriers (*i.e.*, 0·5 per cent).

Data of Klinger.—Klinger also gives a report of the examination of 482 cases of typhoid during convalescence (at the Strassburg station). Fifty-five, or 11·4 per cent., of these excreted typhoid bacilli during convalescence, but not for a longer period than six weeks after defervescence—*i.e.*, temporary carriers. Eight, however, continued to excrete the bacillus beyond this period, and thus fell to be reckoned as chronic carriers (= 1·7 per cent.).

In a later communication, Klinger (1907) notes that, of 604 convalescents examined, he had found 80 temporary carriers (70, or 11·6 per cent., intestinal; and 10, or 1·7 per cent., urinary). Six cases only, or 1 per cent., became chronic carriers. He states that the temporary urinary carriers were all cured by urotropin.

Late Control Examinations.—Another interesting series is reported by Kayser (1907), also of the Strassburg station. This author initiated a late control examination of the typhoid convalescents who had previously been discharged as typhoid-free during the period summer, 1903, to summer, 1905. This late control examination took place after the lapse of at least one year. The potential material for this test was 217 cases, but he was able to recover samples of stools and urine from 101 persons only (= about 46 per cent. of the survivors—33 men, 47 women, and 21 children). There had been 248 cases treated, but 29 of these had died. Of the remaining 219, one had died of another disease, and one had committed suicide. The result of this late examination was that three more carriers were discovered (two females and one male). In the previous year he had examined in conjunction with Brion (Brion and Kayser, 1906) the fæces of 200 convalescents, and obtained a carrier percentage of 1·5. To show the importance of this late control test, the bacteriological findings in two of Kayser's cases may be quoted:

Female (Forty Years).

July, 1904	Primary attack.
August, 1904 (two examinations)	Negative.
October 4, 1905	Negative.
December 7, 1905	Positive.
January 18, February 17, March 9, 1906	Negative.

Female (Twenty-six Years).

August, 1904	Primary attack.
September 23, 1904	Positive.
October 1, 1904	Negative.
December 7, 1905	Positive.
January 18, 1906	Positive.
May 14, 1906	Negative.

In these two cases, therefore, the routine bacteriological tests made in early convalescence, and before discharge, had proved inefficient owing to marked intermittency in excretion. This difficulty is a very serious one, and militates greatly against any reasonably practicable system of bacteriological supervision before discharge. By this late control method, Kayser's percentage of convalescent carriers was raised from 1·5 per cent. to 3 per cent. or 5 per cent. We shall have occasion to refer again to the question of enormously prolonged intermittency in convalescent carriers.

A more recent report by Brückner (1910), on a similarly conducted investigation at the Strassburg Institute, shows clearly the necessity of the late control examination of typhoid convalescents. Kayser's material was derived from the town of Strassburg only, while Brückner also included four suburbs of Strassburg and eleven other townships belonging to his campaign district. The potential sources of material were 566 persons who had had enteric fever in previous years. Of these it was found that 45 (*i.e.*, 8 per cent.) had died, and 170 (*i.e.*, 30 per cent.) had removed elsewhere or were not discoverable. There were thus left 351 persons, and only 35 of these (*i.e.*, 9·9 per cent.) declined to supply material for examination. This percentage would have been still lower had it not been for one small township in which 21 recovered typhoid cases resided, of whom 12 (*i.e.*, 57 per cent.) refused specimens. Brückner remarks that this low percentage of refusals is an index of the public appreciation of the efforts of the typhoid stations. Among the 316 persons whose excreta were examined, 12 carriers were found (= 3·8 per cent.). Of these 316 persons, 104 were children (under fifteen years), and 212 were adults (over fifteen years). One carrier belonged to the former group, and 11 carriers belonged to the latter group. The proportion of carriers among adults was therefore 5·2 per cent.

Perhaps the most thorough bacteriological investigation of typhoid convalescents hitherto reported has been carried out by the Central Research Institute at Kasauli in India, under the direction of Lieutenant-Colonel Semple and Captain Greig, with the assistance of Lieutenant-Colonel Thomson, Captains Harvey, White, Hodgson, and Assistant-Surgeon Paras Ram (Semple and Greig, 1908).

This inquiry was set on foot in 1906 with the object of elucidating the incidence and spread of typhoid in the Indian cantonments, and one of the main problems attacked was the duration of the typhoid bacillus within the human host. In the case of convalescents the observers were not content with the prescribed German routine of two or three final examinations (at intervals of ten days after defervescence) of the excreta before discharge. All their convalescents were examined daily, and many of the cases also, throughout the febrile period as well, until the excretion of the bacillus either ceased spontaneously or became chronic. In their report issued in 1908 they note that eighty-six convalescents had been examined at the Kasauli depot, with the result that no fewer than ten persons were found to be excreting typhoid bacilli in the urine or fæces for periods longer than six weeks after defervescence. This gives the very high percentage of 11·6 of chronic carriers (taking the three-month limit and over as the test for the " chronic " category). This is undoubtedly the highest percentage so far recorded, and may probably be attributed in great measure to the elaborate routine, by which it was scarcely possible to overlook an intermittent carrier. In civil conditions certainly, methods equally thorough would be impossible in practice.

Semple and Greig were working with a more or less homogeneous population—viz., adult males of a definite age group. In order to determine whether this fact would in some measure account for the high percentage of carriers, I have taken the accumulated statistics of Klinger for the German campaign, and determined whether in the age group 23-45 it would be possible to obtain a percentage yielding ten carriers in a small sample of eighty convalescents. The chances of this happening worked out at less than one in a billion, and one must therefore conclude that the high percentage they obtained was most probably due to the thorough routine they adopted.

At the close of Semple and Greig's report is a series of tables in which the results of the daily examinations of eighteen convalescents are detailed. These tables are worthy of careful study, as they show how readily intermittent carriers may be overlooked by a routine limited to three or four examinations during the six weeks following defervescence. An extremely interesting feature is the large proportion of cases in which a prolonged excretion of typhoid bacilli by the urine took place in addition to the more common and better known form of excretion by the fæces. As a rule, however, the bacilluria ceased spontaneously after a time (without the aid of urotropin, which in Semple and Greig's experience proved of little or no value as an inhibiting agent), while the fæces remained either continuously or intermittently infective.

The daily observation of these cases extended over a period of less than six months in each instance.

The writer has had an opportunity of observing several of these invalided army carriers since their return to this country, and of making repeated examinations of their excreta. It has been found, however, extremely difficult to keep in touch with them in civil life. One at least continues (1912) to pass large numbers of typhoid bacilli in the urine.

Tsuzuki (1910) records the results of an inquiry into the question of convalescent carriers in a division of the Japanese army. The circumstances which gave rise to the investigation will be found in the writer's enteric-carrier report (p. 68). The bacteriological part of the work appears to have been carried out with great thoroughness, the tests being made practically every day during convalescence. The result was that three out of fifty-one convalescents in hospital continued to discharge typhoid bacilli beyond the three-month limit—*i.e.*, carrier percentage of 5·8.

Further, a large number of examinations was carried out on (1) persons known to have had enteric previously ; (2) healthy persons belonging to a company in which a recent case of enteric had occurred ; (3) persons occupied in the canteen. In all, 5,109 examinations were made of 2,785 persons, with the following results :

	Known Previous Infection.	No Known Previous Infection.	Total.
Number of persons examined ..	316	2,469	2,785
Number of carriers found ..	6	2	8
Percentage of carriers	1·89	0·08	0·28

The following brief notes are appended with regard to the carriers who contracted their primary infection in 1907 :

1. Fell ill September 2, 1907. Fæces positive on April 17, 1908, and on every subsequent examination up to October 17, 1908, when he was discharged from duty. The urine was also repeatedly positive up to this time.

2. Fell ill September 2, 1907. Urine found to be positive on April 17, 1908, and on all subsequent occasions up to October 17, 1908, when he was discharged from active service. The fæces were never positive. Urotropin had little or no effect.

3. Fell ill July 17, 1907. Fæces positive on June 8, 1908, and with slight intermissions up to October 17, 1908, when he was discharged from duty. Urine never positive.

4. Fell ill November 30, 1907. Fæces and urine positive on April 24, 1908. Examinations of fæces after May 13 were negative, but the urine continued positive till October 23, 1908, when he was discharged from duty.

5. Fell ill September 14, 1907. Fæces positive on May 7, 1908, but all subsequent examinations up to July 17 were negative. Released from isolation.

6. Fell ill August 28, 1907. Fæces positive on April 19, 1908, and on subsequent occasions up to June 30, 1908. Further samples in July, August, and September, were negative. Released from isolation on October 3, 1908.

The remaining two carriers had never had definite clinical symptoms, and might be called " symptomless " carriers. The one had been somewhat out of sorts in August, 1908, but quite fit for duty. On September 2 he had given a positive Widal reaction (1 in 50), and examination of the fæces was positive up to November 30, when he was discharged from service.

The other had absolutely no symptoms. He gave a negative Widal reaction, and the fæces were found positive on two occasions only—viz., July 11 and July 13, 1908. On September 11 he was released from isolation.

Park (1908) examined in May and June, 1908, the stools of fifty-two persons who had had typhoid fever during an epidemic at a lunatic asylum eight months previously. Two were still discharging typhoid bacilli.

He also examined the fæces of sixteen persons who had had typhoid fever at another asylum, and found two of these still positive. They had been well for six months. From this small series, therefore, he obtained a carrier percentage of 6 per cent. A large number of convalescents were examined on leaving hospital, when 5 per cent. were found to be still excreting typhoid bacilli.

Carriers discovered as the Result of Examinations made in the Neighbourhood of Typhoid Patients.

Data of Klinger.—Klinger (1906) of the Strassburg station instituted a bacteriological examination of healthy persons living in the neighbourhood of actual typhoid cases ; 1,700 such persons were examined, with the result that 15 carriers were found during the period July 1, 1903, to March 31, 1905. These carriers were of all ages, from eighteen months to sixty years, and as to sex, 7 were females and 8 males. Of these 15 carriers, 11 had no clinical symptoms either before or after finding the bacilli. In 9 of these 11 carriers the bacilli were found only on one occasion, but in the remaining two they were found three times in the course of a fortnight. All subsequent examinations were negative. Thus, one might provisionally apply the term of "temporary," or, as Klinger suggested, "acute," to these 11 cases (they were 6 males and 5 females). The other 4 carriers were of the chronic type (2 males and 2 females). One had had enteric thirty years before, a second ten years before, while the remaining two were lunatics as regards whose previous illnesses no trustworthy information was available.

Data of Lentz.—The interesting data obtained by Lentz in the course of his examinations of convalescents led him to investigate all relatives and other persons who had been in association with typhoid patients, as well as those persons who in previous years had suffered from typhoid fever. Twenty-two carriers were discovered by this method, 19 of whom were females, and 3 males. The general health of the majority of these carriers was good, but 3 of the females developed gall-stone disease, as was proved by the excretion of small stones in the fæces.

Semple and Greig also record an examination of nursing orderlies who had been in attendance on typhoid cases. Four of these were examined over a long period after they had finished their course, and were about to return to their regiments. None of them ever suffered from enteric fever in a typical form. Two of the men, however, were found to be excreting typhoid bacilli in their fæces. Such cases (probably "transitory" carriers or so-called "acute" carriers of Klinger) are of great importance from the epidemiological point of view, and there is abundant evidence that a proportion of these may pass into the chronic stage.

An extensive inquiry into an outbreak of enteric fever affecting the 71st Regiment of Infantry at the Saint-Brieuc garrison in the summer of 1909 has yielded further evidence showing the enormous importance of the atypical and unrecognized cases. The outbreak has been reported fully in all its aspects, epidemiological, clinical, and bacteriological, by Billet, Le Bihan, etc. (1910). Briefly, the source of infection was stated to have been in all probability contaminated cider, but the chief interest of the inquiry, at least in connection with the subject of this chapter, centres round the bacteriological findings.

There were treated in hospital 142 cases—viz., 33 very severe, 72 moderately severe, 37 benign, with a total mortality of 13, or 9 per cent.

Blood-cultures were made in 74 cases during the first week of the disease, with 57 positive results. Widal examinations were done in 43 cases about the end of the third week, with 40 positive results. The fæces were examined in 129 cases at the end of thirty-five days after entering hospital, with 15 positive results—*i.e.*, 11·6 per cent.

In addition, a careful clinical examination was made of all suspects in the regiment, who showed the slightest symptoms of indisposition, and a surprising proportion of these was found to give either positive Widal tests or typhoid bacilli in the fæces. The clinical histories of these atypical or ambulatory cases are of great interest as showing how insignificant the clinical manifestations of typhoid infection may be. Of 57 such cases examined, 14 only showed a rise of temperature lasting three to five days, 7 lasting two days, while the majority (34) showed complete apyrexia. Some were out of sorts for several weeks, while others returned to their normal condition after only a few days' indisposition. In 8 cases constipation was the only symptom, while in 15 headache, furred tongue, and loss of appetite, were the predominant symptoms. Diarrhœa rarely occurred alone, being generally accompanied by swelling of the spleen, and sometimes rose-spots.

Other symptoms complained of in individual cases were stiff neck, angina, and "rheumatic" pains. The bacteriological results in these cases were as follows :

Cultures were made of the blood of 39 suspects, with 7 positive results; also of 53 men, who lived in rooms where typhoid cases had been most numerous, with 1 positive result. The stools were examined in 64 atypical cases, with 13 positive results—*i.e.*, 20·3 per cent., whereas the percentage of convalescent carriers was only 11·6 per cent. (see above). There is no record of repeated examinations having been made in these cases, but the results are sufficient to show the important part which unrecognized cases may play in the spread of enteric fever. As Semple and Greig had found in their investigations that nursing orderlies were particularly liable to act as transitory carriers, so also in this French garrison a large number (11·4 per cent.) of *infirmiers* showing only ephemeral symptoms of the disease were discharging typhoid bacilli in their stools. Also the conductor of the ambulance in which the typhoid cases were conveyed to hospital gave a positive Widal reaction and positive stools, although he appeared to be an absolutely healthy individual.

OCCURRENCE OF CARRIERS IN A GENERAL POPULATION.

The only data available on the frequency of carriers in a general population are those of Rosenau, Lumsden, and Kastle (1909), in America, and of Minelli (1906) in Germany. The former investigated the question as to how far chronic carriers were responsible for the spread of fever in the district of Columbia.

Three series of examinations were performed:

1. Persons who had had enteric fever in previous years (six months to twenty years previously), and who had been in association with recent cases during thirty days prior to onset.

Thirty-two such persons were examined, with negative results.

2. In the course of enteric studies in special districts, the fæces of 71 persons who had had typhoid fever one to ten years previously were examined, but all were negative.

3. In order to determine how many persons in Washington during the typhoid season were carriers, they examined, from July 16 to November 8, 1,014 samples of fæces, and 26 samples of urine, from 993 persons living in thirty-two blocks of the city.

Out of this large material they found only 3 persons carrying the bacillus who did not present any clinical symptoms of typhoid fever.

The first was a male of fifty years, who had never had typhoid fever. His wife had typhoid fever thirty-eight years ago. There had been no typhoid fever in any house where he had resided, and he had enjoyed good health all his life. Some six weeks before he had been out of sorts, with a feeling of discomfort in the region of the liver (? typhoid cholecystitis). The bacilli were found only once, and he gave a negative Widal reaction. It is unfortunate that no mention is made of the examination of his wife.

The second was a boy of fourteen years. The bacilli were got on one occasion only. No one in the family had had typhoid fever except the boy's mother, who had an attack forty-two years ago. Here also no mention is made of the examination of the mother.

The third was a boy of nine years. The bacilli were found once only in the urine, while the fæces were negative. None of the family had ever had enteric fever, and these were all examined, with negative results.

The percentage found—viz., 0·3 per cent.—accords well with that got by other observers in groups of healthy people associated or not associated with typhoid cases. Minelli (1906) instituted a search for carriers in an institution which had been for years free of typhoid. He chose the town prison of Strassburg, containing 250 inmates. The excreta of all these were examined, with the result that one carrier was discovered. He had been eight weeks in the prison, and asserted that he had never been ill. His serum gave a high Widal reaction (1 in 1,000)—a fact which strengthened Minelli in his belief that the man may previously have had a slight attack of typhoid. He was thirty-seven years old, and, being a vagabond, he may not unlikely have come in contact with typhoid cases.

Minelli's percentage was therefore 0·4.

We shall close these data gathered by individual observers with the report by Prigge (1909) on the carrier statistics at the Saarbrücken Institute.

During the three years prior to 1909 they examined at that institute a total of 10,841 persons, and discovered 84 carriers, which are classed simply into two groups : (1) Temporary carriers who discharge bacilli up to one year, and (2) chronic carriers who discharge for a longer period than one year.

There are good grounds for extending, as Prigge does, the time limit from three months to one year in the case of temporary carriers, as doubtless, even admitting the difficulty entailed by intermittency, a considerable proportion of convalescent carriers who have passed the three-month limit may cease to discharge spontaneously long before a year has elapsed, and therefore do not deserve the appellation "chronic" in the ordinary sense of that term.

In the first group he classes—

1. Persons in whom the bacillus was found before clinical symptoms arose—*i.e.*, primary carriers (Conradi), or *porteurs précoces* (Sacquépée).

Three such carriers were discovered in whom the symptoms did not supervene till eighteen, nineteen, and twenty days afterwards. Two of these cases were children, and the third was an adult man.

2. Clinically cured persons who continued to discharge bacilli from ten weeks to one year after the attack.

There were twenty-five of these—viz., 9 men and 16 women.

3. Healthy persons—24 (16 men and 8 women).

In the second group he classes—

1. Persons who have previously had enteric fever—27 cases. The proportion of females to males in this small series Prigge does not state, but he notes that in a larger series of 102 cases, taken from the whole campaign district, 17 were males and 85 females, thus showing the enormous preponderance of female chronic carriers.

2. Persons who have never had typhoid fever—8 cases, all women.

The difficulty of obtaining accurate past histories in these cases is, as other observers have found, very considerable, and there is little doubt that some at least of these cases may have had enteric fever in a slight or atypical form.

General Statistics from the German Campaign Area, including Data on the Age and Sex of Carriers.

We come now to consider the carrier statistics compiled for the whole campaign district of South-West Germany from the commencement of the campaign up to the end of the year 1907. These have been very fully worked out and commented upon by Klinger (1909). The population of the district (excluding the Bavarian Pfalz) was at December 1, 1905, about 2,300,000.

Up to the close of 1907, 431 notifications of transitory and chronic typhoid carriers were made (three months being taken as the upper limit for a transitory carrier). These are arranged in the annexed table (reproduced from Klinger's report) according to age and the occurrence or non-occurrence of a definite primary infection.

Carrier Statistics (German Campaign).

Age Groups.	Chronic Carriers.						Transitory Carriers.					
	Previous Typhoid.			No Previous Typhoid.			Previous Typhoid.			No Previous Typhoid.		
	M.	F.	Total.	M.	F.	Total.	M.	F.	Total.	M.	F.	Total.
0-2	—	—	—	—	—	—	1	3	4	3	2	5
2-5	1	—	1	1	—	1	1	2	3	4	6	10
5-10	1	2	3	—	1	1	4	9	13	11	11	22
10-15	—	1	1	—	2	2	3	2	5	8	5	13
15-20	2	4	6	—	—	—	2	11	13	4	10	14
20-25	4	4	8	—	3	3	9	5	14	2	3	5
25-30	1	13	14	1	3	4	2	6	8	7	5	12
30-35	2	21	23	1	2	3	—	3	3	2	4	6
35-40	3	18	21	—	6	6	2	9	11	6	1	7
40-45	6	21	27	—	3	3	1	6	7	3	2	5
45-50	1	18	19	—	2	2	—	1	1	2	4	6
50-55	4	12	16	1	3	4	2	1	3	2	3	5
55-60	1	7	8	—	6	6	3	3	6	1	1	2
60-65	2	13	15	1	2	3	—	—	—	1	1	2
65-70	2	3	5	—	1	1	—	—	—	1	—	1
70-75	—	—	—	—	2	2	—	—	—	—	—	—
75-80	2	3	5	—	1	1	—	—	—	—	—	—
80-85	1	1	2	—	—	—	—	—	—	—	1	1
?	—	2	2	—	2	2	1	—	1	1	2	3
Totals	33	143	176	5	39	44	31	61	92	58	61	119

There were thus 220 chronic carriers and 211 transitory carriers. Of the former the great majority (80 per cent.) gave evidence of a primary infection, while in only 43·6 per cent. of the transitory carriers was this evidence forthcoming.

Sex of Carriers.—The enormous preponderance of female chronic carriers over male is strikingly brought out—viz., 182 to 38, or nearly 5 to 1—whereas among the transitory carriers the proportions are very nearly equal (female to male, 1·4 to 1).

Gall-stone troubles were definitely diagnosed in 30 chronic carriers—*i.e.*, 13·6 per cent. This figure corresponds closely to the percentage of gall-stone cases (of all origins) in which diagnostic symptoms are present.

Perhaps the most important and striking feature brought out by the table is the different distribution of the transitory from that of the chronic carriers according to age groups. Whereas among the transitory carriers young persons form the great majority, among the chronic carriers persons in middle age or advanced life predominate markedly.

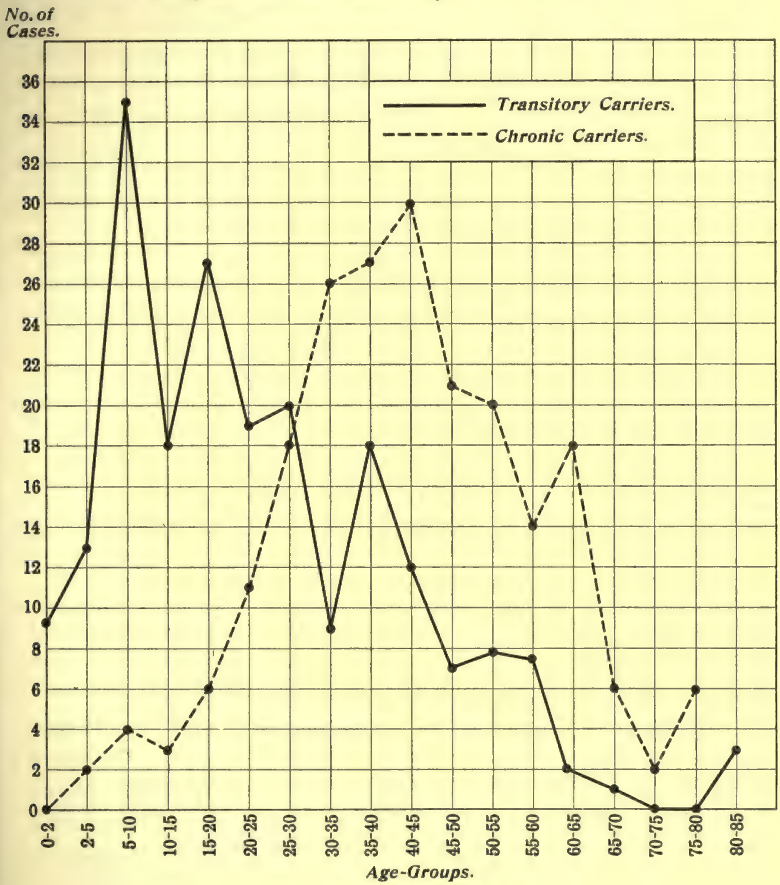

FIG. 1.

This is shown more clearly in the annexed curve in which the maximum point for the transitory carrier is reached at the five to ten age limit, and that for the chronic carrier at the forty to forty-five age limit. It is important to note, however, that the curves indicate only the actual incidence on the several age groups, and not the proportional incidence.

It will be obvious, also, from the table that no data are supplied on which to base a relation between the carrier output and the age at which the typhoid infection takes place. When a chronic carrier with a history of previous typhoid infection is discovered, it is not the present age of the carrier which determines the age group in which he should be enrolled, but the age of the carrier when he recovered from the infection—*i.e.*, on the assumption that no reinfection has taken place in the interval. Accurate data on this point will be available only when large numbers of carriers have been examined continuously from convalescence onwards.

With regard to the period during which these carriers have been under bacteriological control since they passed the three-month limit, 30 were examined up to six months, and the others from one year to two, three, four, and four and a half years.

Included in the 220 chronic carriers are some 30 cases in which the primary infection took place four to thirty years previously.

A spontaneous cessation in the excretion of the typhoid bacillus occurred in 42 of these chronic carriers, sometimes, indeed, after prolonged positive periods, but, as Klinger remarks, such bacteriological cures must be regarded with considerable scepticism in view of the prolonged intermittent periods which have been observed, and the not unlikely possibility of the transmission of a false sample.

During 1906 and 1907, 38 typhoid convalescents, or 1 per cent. of the total number of typhoid cases (3,867), became chronic carriers. The percentage is thus much smaller than that obtained by individual observers.

Further facts with regard to the campaign, particularly during the earlier years 1904, 1905, and 1906, are given by Frosch (1908). There was a total of 6,708 enteric cases in that period (beginning of 1904 to end of 1906), and of these 310 became carriers; 166 excreted the bacillus for three months or longer—*i.e.*, 2·47 per cent. (=Dauerträger); and 144 excreted the bacillus for a period under three months—*i.e.*, 2·15 per cent. of transitory carriers (=Bazillenträger).

In Frosch's series females again formed 82 per cent. of the chronic carriers, and 60 per cent. of the transitory carriers, while children (up to fifteen years) formed only 4 per cent. of the chronic carriers, but 35 per cent. of the transitory carriers.

An interesting point with regard to the occupations of the female typhoid cases is brought out from Frosch's figures. For the year 1906 the total number of typhoid cases in the district was 2,080 (938 males, 454 females, and 688 children up to fifteen years). Of these 454 females no fewer than 314 were "Hausfrauen," while 56 were domestic servants. Thus 370, or 81 per cent. of the female cases, were engaged in housework, and from these the great majority of the chronic carriers, and more than half of the transitory carriers, were recruited.

We shall deal with the significance of this fact when we come to consider the pathogenesis of the carrier state (*vide* p. 74).

The data for the Bavarian Pfalz have been compiled by G. Mayer (1910).

In July, 1903, Bavaria decided to join in the campaign that had been begun in the neighbouring districts of South-West Germany, and erected two institutes at Landau and Kaisersläutern respectively. G. Mayer directed the latter up to February 1, 1908. The population of his district was about 400,000, and the number of typhoid cases was about 930 during the period (1904 to 1907).

Typhoid carriers to the number of 151 were found—viz., temporary (under three months), 73 ; chronic (over three months), 78. Of the temporary carriers 54·9 per cent. were women, and 57·4 per cent. children ; while of the chronic carriers 65·5 per cent. were women, and 25·2 per cent. children (up to fifteen years).

Nine of the chronic carriers (or, roughly, 10 per cent.) suffered from gall-stone trouble, while three had severe "bilious" relapses after three, six, and ten years respectively.

According to the carriers' own statements, 16 of them had never been ill, 10 had had enteric fever four to nine years previously, and 2 of them had had enteric fever twenty to thirty years previously.

We close this section with some interesting data collected by Conradi and Klinger bearing on the relative infectivity of typhoid patients during the incubation period, and the course of the disease.

These data, it is claimed, show the relatively high infectivity of typhoid patients during the incubation stage and the earlier weeks of the disease.

The material at Conradi's disposal for the investigation of this question was derived from the data relative to certain groups of cases carefully selected from the total of 600 cases investigated during a period of two and half years, at Saarbrücken. In calculating the date on which the primary case infected the secondary, he took the interval between the beginning of the primary case and the beginning of the secondary and subtracted therefrom ten days.

In Table I. are recorded the data relative to 38 contact infections (secondary cases) which took place in various families in spite of the fact that the respective primary cases had been removed to hospital. As a rule twelve days elapsed between the beginning of the disease and the removal to hospital. On the day after removal the house was thoroughly disinfected. Conradi considers that the table shows that the great majority of the secondary cases must have received their infection from the primary cases, while the latter were still in the early days of their illness.

In Table II. are given the data with regard to a series of secondary cases which arose in families in spite of disinfection and isolation of the primary case in the house. Satisfactory isolation was admittedly difficult in many cases, so that there may have been some opportunity of infection after the twelfth day, when disinfection was as a rule performed.

In Table III. are given the data relative to secondary cases due to primary cases not treated by a physician.

TABLE I. (CONRADI, 1907*c*).

Data relative to 38 contact infections which took place in various families in spite of the fact that the first person attacked was removed to hospital.

Infected	by	primary case during	1st	week of disease,	25	secondary cases.
,,	,,	,,	2nd	,,	7	,,
,,	,,	,,	3rd	,,	4	,,
,,	,,	,,	4th	,,	1	,,
,,	,,	,,	5th	,,	1	,,

TABLE II. (CONRADI, 1907*c*).

Data relative to 28 contact infections which took place in families in spite of disinfection and isolation of the primary patient in the house.

Infected	by	primary case during	1st	week of disease,	14	secondary cases.
,,	,,	,,	2nd	,,	7	,,
,,	,,	,,	3rd	,,	2	,,
,,	,,	,,	4th	,,	2	,,
,,	,,	,,	5th	,,	1	,,
,,	,,	,,	6th	,,	1	,,
,,	,,	,,	7th	,,	1	,,

TABLE III. (CONRADI, 1907*c*).

Data relative to 19 contact infections due to typhoid cases not treated by a physician.

Infected	by	primary case during	1st	week of disease,	10	secondary cases.
,,	,,	,,	2nd	,,	2	,,
,,	,,	,,	3rd	,,	4	,,
,,	,,	,,	4th	,,	2	,,
,,	,,	,,	5th	,,	1	,,

These 85 *contact infections may be thus summarized, ten days being taken as the most probable incubation period.*

Infected by primary case during	1st	week of disease,	49	secondary cases.
,, ,, ,,	2nd	,,	16	,,
,, ,, ,,	3rd	,,	10	,,
,, ,, ,,	4th	,,	5	,,
,, ,, ,,	5th	,,	3	,,
,, ,, ,,	6th	,,	1	,,
,, ,, ,,	7th	,,	1	,,

It will be seen that 58 per cent. of the observed contact infections took place during the first week of the primary infection, and, in view of the facts that have been ascertained with regard to the infectivity of the incubation stage, Conradi considered it probable that a considerable proportion of these may have become infected during the incubation stage of the primary case.

The table compiled by Klinger (1909) from the data relative to the two years 1906 and 1907 of the typhoid campaign in South-West Germany affords a striking illustration of the importance of the primary carrier, in the spread of enteric fever.

The material employed was a series of 812 contact infections, two weeks being taken as the average incubation period. In 60 cases Klinger believed that he had ascertained the incubation period with tolerable certainty; he found it to vary from five to forty-five days, with an average of sixteen days. Also, in the course of a water-borne epidemic, he had found that 98 per cent. of a series of 83 cases, regarded as having been infected at the same time, developed clinical symptoms eleven to eighteen days later.

Statistics of Contact Cases (Klinger).

	Contact Cases.		Total Contact Cases.
	1906.	1907.	
Incubation Period:			
1st week	18	15	33
2nd ,, ...	84	66	150
Course of the Disease:			
1st week	104	83	187
2nd ,, ...	87	71	158
3rd ,, ...	58	58	116
4th ,, ...	16	43	59
5th ,, ...	13	21	34
6th ,, ...	7	15	22
7th ,, ...	9	5	14
8th ,, ...	9	7	16
9th ,, ...	10	5	15
10th ,, ...	5	3	8

Klinger admits it would be a mistake to place too much reliance on the accuracy of the figures, in view of the variations in the incubation period; nevertheless, he takes the view that, regarded as a whole, the figures show that a preponderant number of contact infections take place during the early period of the typhoid infection, or, in other words, that a typhoid patient is most dangerous during the incubation period and the first and second weeks of the disease—*i.e.*, during the period when little or no precautions can be taken. In the later stages of the disease, the gradual cessation in the excretion of the specific bacteria and the precautions taken as to disinfection, etc., serve to keep the contact infections at a relatively low figure.

III. INSTANCES OF INFECTIVITY OF CARRIERS.

House and Street Cases.

The influence of carriers in maintaining the endemicity of typhoid fever in individual houses and streets, or groups of houses in isolated country districts, has been abundantly attested by the work of recent years, and in no other sphere has the search for carriers been more fruitful. Indeed, so many instances of the dangers arising from carriers in this connection have accumulated that it will be possible to refer in detail only to a few of the most striking and illustrative examples. For further instances and references the reader is referred to the Local Government Board Report on this subject by the writer.

I shall commence with the now well-known case of the Strassburg baker's wife, reported six years ago by Kayser (1906).

On May 20, 1904, an apprentice, lodging with the master-baker's wife, a woman forty years of age, contracted typhoid fever, and died during the third week of the disease. The baker's wife was known to have had typhoid fever ten years previously. In recent years it had been observed that practically every fresh apprentice became ill shortly after his entering on residence with her, with symptoms pointing to stomach and bowel disorder. These symptoms were attributed by the baker's wife to "too good diet." On May 26, 1904, this woman was discovered to be a carrier, and further examination of her stools on June 1, June 3, June 22, and July 5, proved positive. From July 19 onwards, however, weekly examinations of her stools gave negative results; but there was a strong conviction that the samples received from her were not her own.

On August 8 her tenant, a man twenty-nine years of age, who used the same water-closet as the baker's wife, took ill, and died in the third week of the disease. Under police pressure the woman was now brought to the clinic, and her stools were found to contain enormous numbers of typhoid bacilli.

In a later communication, Kayser (1907) attributes another case of typhoid fever to infection from the baker's wife.

Thus three cases occurred in the household of this woman.

Rosenthal (1906) in Göttingen gives an interesting description of repeated cases in one household attributable to a carrier.

During the autumn and winter of 1905-06 there had been four cases of typhoid fever in a single household, and the fæces of thirteen inhabitants of this house were examined, with the result that one female carrier (forty-two years) was discovered. She had not been ill for years, but there was some evidence of her having passed through an attack of typhoid fever in 1878. In that year she had had a severe febrile attack, and at the same time her son had a severe intestinal trouble. During that year also an epidemic of typhoid fever had broken out in her street. On inquiry it was found that from 1897 to 1906 thirteen cases of typhoid fever were in all likelihood attributable to personal intercourse with this woman. Six of these persons were lodgers who got breakfast and supper from her; three were children who lived in the house; one was a female neighbour, who often visited her; and three were persons in neighbouring houses who got their vegetables from her. This woman and her husband sold vegetables and fruit, and attended the markets three times a week. She may therefore have infected many more people. Rosenthal also notes that the excreta from the house were used to dung the vegetables. Necessary precautions were now enforced with regard to disinfection of excreta, but there was no power to prevent the woman plying her trade.

Mention may be made of a well-known case reported by Soper (1907) of New York, in which a female carrier in the person of a cook was found to have been responsible for the occurrence of no fewer than twenty-six cases of typhoid fever in seven different families.

This female carrier ("Typhoid Mary") has, we think, earned an entirely undeserved newspaper notoriety in America.

The outbreak attributable to this cook, and which led to her detection as a chronic carrier, occurred in the first two months of 1907, while she was in service in a New York family, the victims being a chambermaid and a daughter of the house, who died (the only fatal case in the series). The cook had been two months in this family before the cases arose. On March 19, 1907, this woman, after a severe struggle in which police aid had to be requisitioned, was conveyed to the detention hospital, under charge of Drs. Wilson and Park, and there her fæces were bacteriologically examined, with a positive result. Much difficulty was experienced in tracing out the past history of this cook, and possibly the achievements now to be mentioned have no claim to be exhaustive. Considerable gaps in her history could not be filled up, in spite of careful inquiry.

The various outbreaks occurred as follows :

September, 1900 : *Mamaroneck.*—During a summer residence in this place a visitor to the family developed typhoid fever. It is remarkable that the cook had been three years in this family without having given rise, so far as is known, to any case of the disease.

December, 1901 : *New York.*—One month after the cook's arrival in this family a laundress in their employment developed typhoid fever.

Summer, 1902 : *Dark Harbour.*—Seven members of the family and two servants developed typhoid fever. All the servants except the cook had been employed in this family for one month or more in New York before leaving for the summer residence in Dark Harbour. The cook had been engaged specially for the summer, and had joined the family three weeks before it left for Dark Harbour.

Summer, 1904 : *Sands Point.* — Four servants developed typhoid fever. The cook had been nine months in the service of the family without any untoward occurrence. The cases arose when the family removed to Sands Point, and the servants were practically new hands (laundress, gardener, butler's wife, and butler's wife's sister).

Summer, 1906 : *Oyster Bay.*—Six cases occurred in one household.

September to October, 1906 : *Tuxedo.*—One laundress took ill fourteen days after the arrival of the cook.

January to February, 1907.—Final outbreak at New York (already quoted).

In a further report on this case, Park (1908) mentions that the cook had been kept in detention since she was discovered to be a carrier, and that various intestinal antiesptics had been employed with a view to cure, but without success. Her urine was always negative.

Several household endemics attributable to carriers, and persisting over a long term of years, have been reported (Niven, 1908 ; Huggenberg, 1908 ; Hilgermann, 1908, etc.). In the instance reported by Huggenberg, thirteen cases in all occurred in one family during the period 1877 to 1908—viz. :

Mother : May, 1877.
Father : July, 1886.
Son : September, 1892.
Female servant : February, 1899.
,, August, 1899.
,, September, 1900.
,, August, 1902.
Daughter-in-law : September, 1902 (had been living for some weeks in the family).
Female servant : February, 1903.
,, October, 1903.
,, December, 1904 (this servant was living in the same house, but with another family).
,, June, 1905.
,, February, 1908.

Huggenberg made a bacteriological examination of the excreta of all the members of the family, and was able to demonstrate typhoid bacilli in those of the mother, who had had her primary attack of enteric fever thirty-one years before. Her serum also gave a well-marked Widal reaction.

Some interesting points find illustration in the following two cases reported by Kayser (1909) :

Case 1.—Where the medium of transference was, in all probability, foodstuffs.

Frau B. went to a neighbouring town to attend Frau J. in childbirth. Some of the latter's family had had typhoid fever three months before, but all of these during convalescence had been declared typhoid-free. On her return home from attendance on Frau J., Frau B. took with her some fruit and pastry, of which she and her husband partook. The husband shortly afterwards developed typhoid fever, and Frau B. was for some days out of sorts, but there was no reason to suspect that her illness was typhoid fever. The household of J. was examined, and Frau J., who was quite well, was discovered to be a carrier.

Herr B. after his attack also became a chronic carrier, and received instructions with regard to the disinfection of his excreta. After the middle of February, 1907, he neglected to take the prescribed precautions. In March, 1907, Frau B. had an accident to her abdomen, followed by what was thought to be a traumatic perityphlitis, but which proved to be typhoid fever. In Kayser's view the trauma was probably a factor which predisposed to the contraction of the fever (*vide* p. 74).

CASE 2.—This case is also interesting as showing how important it is to see that the disinfection of excreta is properly carried out by persons who are found to be carriers.

A shoemaker's wife, Frau E. (fifty years), was discovered to be a chronic carrier in September, 1905. In July, 1905, a daughter, and in August-September an adult, son of Frau E., had contracted typhoid fever. The woman objected to the disinfection of her stools, and resented interference with her domestic arrangements. Near her house lived a young married daughter of hers, who frequently visited her along with her child. The latter took ill in September, 1905, and died, and the daughter herself took ill and died in June, 1906.

Brückner (1910) records another instance of a female carrier who refused to carry out her instructions. For some years she had been under observation as a carrier, but cases attributable to her continued to crop up from year to year, and in 1909 had reached the respectable total of thirteen, including one fatal case.

This woman decidedly refused to take hygienic precautions, and will therefore remain a standing danger to the community.

The part played by carriers in maintaining the endemicity of enteric fever in country districts is further exemplified by the series of cases reported by Watt, Medical Officer of Health, Aberdeenshire, 1909, in his report on the health of the county for the year 1908. My thanks are due to Dr. Watt for kindly supplying me with additional data. The history of one of these cases may be given :

A female carrier (aged sixty-five years) was discovered in connection with a case of enteric fever on a farm ("S") in Aberdeenshire in August, 1908. The person attacked was the farmer, who died, and the carrier was his housekeeper. This woman had had enteric fever in 1900, while a patient in a lunatic asylum (see account of carrier cases in this asylum, p. 51). Soon after her recovery from the fever, which was a severe one, she was discharged from the asylum, and went to reside at a farm ("B") for a short time. At this farm an outbreak occurred, and it was ascertained that this woman had been living at the farm when the first case occurred there. Subsequent outbreaks occurred in places where she was employed as cook or cook-housekeeper:

Hotel in "R," 1901, October, three cases.

Farm "A," 1902, April, three cases.

Also, at another house where she was in service during 1902, the master and his daughter were attacked by an illness which, in the light of subsequent events, may be regarded as having possibly been typhoid fever, though not diagnosed as such.

Farm "O," 1905, January, two cases—farmer and his son.

Farm "F," 1907, August, two cases—male servants.

It is interesting to note that, in view of the danger arising to the community from this woman, the local authority, with the consent of the Local Government Board for Scotland, resolved to grant her an allowance of five shillings a week until she reached the age when she would be entitled to a pension, on condition that she did not engage in any work involving the handling of food. The offer was accepted.

Irwin and Houston (1909) of Belfast have put on record a series of typhoid infections due to a female urinary carrier. She had had enteric fever seven years previously, when she was a servant in a family at Liscard. Since her illness she had not enjoyed good health, and complained of frequent headaches and gastric disturbances. After her recovery from the fever she took another situation in Liscard, but she had not been a month in her new post before the master of the house developed enteric fever. During the next two years she was in different situations, but nothing of importance occurred. She then went to Liverpool, and while serving in a family there the son of her mistress developed enteric fever. Finally she went to Belfast, and while she was in service in that city four people living in the same house with her developed typhoid fever. In seven years, therefore, six people living in the same houses with her had contracted this disease. The urine of this woman contained large numbers of typhoid bacilli, but the fæces were negative. Her serum gave an incomplete Widal reaction.

Walker Hall and Roberts (1911) also record the case of a female urinary carrier (aged thirty-four) who had enteric fever in July, 1905. Since that date no fewer than eight cases of infection have been traced to her. Thus, in September, 1905, her sister developed typhoid, in December her brother and her father; in July, 1907, another sister; in July, 1908, a parlourmaid and a housemaid in a house where the carrier was cook; in September, 1908, a kitchenmaid in the same house, and in December, 1908, a nurse who attended to the carrier in hospital. Since January, 1909, she has been under the constant bacteriological supervision of Professor Walker Hall, whose observations on the effect of treatment will be referred to in another section (*vide* p. 100).

Recently Johnstone (1910*a*) has reported to the Local Government Board on the association of carriers with endemic typhoid fever in a small Buckinghamshire hamlet. This hamlet (Jennet Hill) consists merely of a few cottages distributed in two groups: (1) A row of ten dwellings known as Lailey's Row, facing upon a cul-de-sac off the main-road between Stanford Dingley and Clay Cross; and (2) nine dwellings scattered irregularly along the same road in the direction of Stanford Dingley and in the direction of Clay Cross. The population of Jennet Hill itself is not more than 80 persons; and if the neighbouring hamlets of Stanford Dingley, Clay Hill, and Bucklebury Common, be added, the population of Jennet Hill and its vicinity probably does not amount to 400.

During the period 1893 to 1907, 36 cases of enteric fever were notified from the rural district outside the vicinity of Jennet Hill, with a population of about 15,000, while from Jennet Hill itself and its vicinity 26 cases were notified. During the period 1896 to 1907, 25 cases were notified from Jennet Hill and its vicinity, while only 24 were notified from the remainder of the rural district. Jennet Hill itself, with a population of 80 people, supplied no fewer than 16 of these 25 cases.

The following table shows the number of cases of enteric fever year by year in the vicinity of Jennet Hill and in the remainder of the rural district of Bradfield, respectively, during the period 1893 to 1907 :

	Jennet Hill.	Rest of Rural District.
1893	1	1
1894	—	4
1895	—	7
1896	4	1
1897	8	2
1898	2	3
1899	5	2
1900	1	2
1901	—	6
1902	2	2
1903	—	—
1904	3	—
1905	—	3
1906	1	1
1907	4	2

A marked lack of correspondence between the two parts of the rural district is evident in most years, especially in 1894, 1895, 1897, and 1901 ; and although the total number of cases was small, the discrepancy suggested the existence of some influence which affected more particularly the neighbourhood of Jennet Hill.

In 1908 an inquiry was made by Dr. Johnstone with a view to ascertaining the cause of this special incidence of enteric fever on Jennet Hill, and in this connection attention was at first mainly directed to water-supply, milk-supply, uncooked foods, mineral waters, and excrement disposal. The evidence on these points must be consulted in the original, but it is sufficient to note here that no satisfactory solution of the excessive incidence of enteric fever on Jennet Hill was reached as the result of this inquiry.

The question then arose as to the possibility of carriers playing a part in the dissemination of enteric. Particular attention was directed to Lailey's Row, as only four of the ten houses composing this row had escaped the fever. Moreover, three of these four houses had but few inhabitants, and these of an age which would render them little susceptible to the disease. Circumstances connected with the occurrence of further cases of enteric fever in 1909, at Lailey's Row, and also in relation with a family that had until recently resided there, strengthened the suspicion that a carrier might be the disseminating agency of the disease. On March 27, 1909, a boy of six, living at No. 8, Lailey's Row, developed enteric fever. This boy came to Jennet Hill in October, 1908, with his family, consisting of father, mother, and another brother aged fourteen. He had not been in contact with any known case of enteric fever, and he had partaken of no suspicious food or drink.

The former occupants of No. 8, Lailey's Row had gone to a house about three miles away, and two persons were notified as suffering from enteric fever shortly after their return (March, 1909) from a visit to this house.

In May a child of one year, residing at No. 9, Lailey's Row, took ill. She had been in this house since October 18, 1908. The symptoms were obscure, but not inconsistent with a diagnosis of typhoid fever, although examination of the stools in the third week after onset was negative.

In the meantime endeavours were being made to obtain samples of excreta (fæces and urine) and samples of blood from the inhabitants of Jennet Hill, and especially from those living in Lailey's Row. Great difficulty was experienced, but ultimately samples of fæces and urine were got from 18 persons, 14 of whom resided in Lailey's Row, also a sample of fæces from another person who formerly lived in No. 8, Lailey's Row. Blood-samples were received from 15 persons, all residing in Lailey's Row. These samples were examined by the writer. None of these persons were known to have had enteric fever. Six, however, gave a positive Widal reaction (1 in 100), while one gave a partial reaction (1 in 50). Four of the samples of fæces contained typhoid bacilli in large numbers, and repeated examinations of these were made :

A. Positive on May 13, 1909, June 18, July 3. Negative on June 4 and July 16.

B. Positive on June 4 and July 16.

C. Positive on June 4 and July 16.

D. Positive on May 18, June 2, July 9. Negative on July 24.

The sera of A, B, and D, gave a negative Widal reaction, while that of C gave a positive reaction.

The carriers A, B, and C, belonged to one family, being mother, father, and son, respectively. The mother presented no history of enteric fever. In 1888 she came to reside at Clay Hill, next door to the house in which a case occurred in 1893. She stated that while at Clay Hill her husband (B) and her two sons, one of whom was C, had enteric fever in April, 1891. In October, 1893, she removed to No. 9, Lailey's Row, but no cases were notified from Jennet Hill till July, 1896. There may have been unrecognized cases, however. From 1896 onwards cases continued to crop up in Lailey's Row and its neighbourhood, seven of them occurring in the houses next door to A.

The husband and son were both difficult persons to deal with, and there was doubt as to whether the samples of fæces received from them were samples of their own fæces or of the mother's fæces.

The carrier D was a married woman who came to Lailey's Row in September, 1903. She had no history of enteric fever, nor was there any history of enteric fever in families with which she had lived as a domestic servant. In her own family no case of enteric fever is known to have occurred until October, 1906, when her husband was attacked. Two cases (see above) occurred in connection with the house she had occupied since leaving Lailey's Row.

As only a limited number of examinations was practicable, it appeared possible that there might be other carriers at Jennet Hill, although the detection of two undoubted carriers, as well as of two persons in whom the presence of this condition is not yet free from doubt, is sufficiently remarkable in so small a community.

The writer has been informed (March, 1912) that another case of typhoid fever has occurred in the household of the carrier D. This woman was confined in February, 1912, and now her daughter, born three years ago, has developed enteric. The Medical Officer of Health (Dr. J. R. Prior) tells me that since the carrier was informed of her condition she has been scrupulously careful and clean. The earth closet is also excellently kept. A sample of her fæces was examined in March, 1912, with positive result. It is of some interest that the two cases of enteric fever which were notified in March, 1909 (see above), were a sister and niece of the carrier D. This sister had just returned home after nursing D in childbirth. These facts at least suggest the possibility that during confinements hygienic precautions may be somewhat relaxed.

Many instances of the intermittent infectivity of carriers have been met with, but some data may be given here which tend to show that, though infections appear to be particularly frequent among persons coming for the first time into contact with carriers, there are numerous cases showing that persons who have been a very considerable time in association with a carrier may suddenly contract infection.

Thus, one of Hilgermann's carriers (a female), after a lapse of five years after her primary attack, infected two persons, with one of whom she had had constant social intercourse. Another carrier (two years after her primary attack) infected her nephew, who had been a year with her in the house. Also a case of marital infection occurred on this occasion through the agency of a female carrier. This woman had caused, in 1904, a severe outbreak of typhoid fever in the Bavarian Pfalz. Three years later her husband contracted the fever. It appeared that this woman had managed to escape the continual supervision of the typhoid station by frequently changing her abode. She had apparently paid no attention to instructions as to disinfection.

Similar cases of marital infection have not infrequently been recorded, and it would appear that in some instances at least the carrier state may not have been acquired as the result of any obvious precedent infection. Mayer (1908) records such a case :

On September 23, 1902, a servant girl in " D " entered on her service in the place of a sister who was ill with typhoid fever and in hospital. Later, on October 5, this girl herself contracted typhoid fever. After some years she married a certain Johannes H. in " O." A small epidemic occurred in this hamlet, and there was an investigation, with the result that both Johannes H. and his wife were found to be chronic carriers. The husband, so far as he could remember, had never suffered from any abdominal disturbance, and the only conclusion that could be arrived at was that he had become a temporary carrier as the result of association with his wife, who after her attack in 1902 continued to excrete typhoid bacilli. From being a temporary carrier he had developed into the chronic stage.

We have to bear in mind not only the possibility of marital cases like the above, but also of the occurrence of multiple carriers in a single family. Fornet (1909), who has recently employed this fact in support of his view that the carrier state is an immunity phenomenon, reports that in the course of the typhoid campaign in South-West Germany, no fewer than twenty-six families were discovered, in which at least two, and sometimes three, members were carriers.

I shall discuss in a later section (p. 75) Fornet's view as to the nature of the carrier state, and the evidence he adduces in support of his view; but I may explain here that his belief is that the carrier state is the consequence of a symptomless reinfection, and that the bacilli shed by the chronic carrier may not necessarily be the lineal descendants of the strain which caused the primary infection. The multiple occurrence of carriers in families he would explain on the assumption that all were similarly exposed both to the conditions which rendered the primary infection possible, and to those which resulted in the second or symptomless infection, culminating in the carrier state.

Milk-borne Cases.

In the foregoing section illustrative cases have been recorded of small outbreaks of enteric fever in individual houses or neighbouring groups of houses, due to association, of diverse kinds, with carriers.

The transmission of infection from the carrier to the healthy has been in many cases through foodstuffs contaminated by the carrier; but the exact history of the infective agent in its passage to the new host, especially in the absence of cleanly personal habits either on the part of the carrier or his or her associates, cannot in all cases be satisfactorily determined.

In the milk-spread cases which have been recorded during the last few years, the infection has taken hold of comparatively large groups of cases, and has been of a more or less explosive character.

The instances we propose to bring forward have been reported mainly by British workers, whose respective inquiries have been made on so exhaustive a scale as to satisfy the most captious epidemiological critic. We are of opinion that these milk-borne outbreaks associated with carriers afford, perhaps, the most trenchant evidence of the infectivity of the carrier.

Other instances besides those to be detailed in this chapter will be found in the Local Government Board Report by the writer.

Perhaps the most fully investigated case of carrier infectivity through the medium of a milk-supply is that reported by Johnstone in 1910 in connection with enteric prevalence in Folkestone.

The following is a brief survey of the inquiry :

The Urban District of Folkestone had at the census of 1901 a population of 30,379, and in the middle of 1908 it was estimated to be 35,580. In the year 1901 Dr. Theodore Thomson had reported to the Local Government Board on recurrent enteric fever in that district, and had made careful inquiry into water-supply, refuse and excrement disposal, sewerage and drainage, and the conditions prevailing in the various cowsheds, dairies, and milk-shops. He found that no satisfactory explanation of the repeated occurrences of enteric fever in Folkestone could be obtained by a consideration of the water-supply and other sanitary conditions. He was able, however, to show that in certain years—viz., 1896, 1897, 1899, and 1900—milk was a prominent factor in the dissemination of enteric fever in Folkestone, while it may have been responsible for a small share of the fever in 1898. He also noticed that a certain milker had worked upon the three different milk-farms which were associated with the dissemination of enteric fever in the years 1896, 1897, and 1899. At that time, however (1901), there was no knowledge of the typhoid carrier, and Dr. Thomson had dismissed the coincidence with the remark that " no milkman, even if uncleanly in his ways, can convey infective material unless the material be there to convey." Dr. Johnstone, who took up the inquiry in August, 1909, found that the facts elicited by Dr. Thomson with regard to water-supply and general sanitary conditions still held good, and proceeded to inquire into the milk question.

Before detailing his results, we append tables (extracted from Dr. Johnstone's report) relative to the incidence of enteric fever in Folkestone from 1893 to 1909.

From the figures it will be seen that enteric fever began to increase in Folkestone Urban District in 1896, and that it attained its maximum prevalence in 1899, subsiding in 1901, to show minor recrudescence in 1902, 1903, 1907, and 1909. No correspondence can be traced between the degree of prevalence of the fever in the other districts and that in Folkestone.

N.B.—In considering these figures, it has to be borne in mind that, at the census of 1891, females to males in Folkestone were as 138 to 100, whereas in England and Wales the proportion was 108 to 100. At the census of 1901, females to males in Folkestone were as 136 to 100, and in England and Wales as 107 to 100.

Table showing the Number of Deaths from Enteric Fever, and the Number of Cases notified, in the Ubran District of Folkestone during the period 1893 to 1909.

For comparison, similar figures are given for the neighbouring Urban Districts of Hythe (population 1901, 5,551), Sandgate (population 1901, 2,294), and Cheriton (population 1901, 7,091), and for the Rural District of Elham (population 1901, 6,813).

	Folkestone Urban District.		Hythe Urban District.		Sandgate Urban District.		Elham Rural District.		Cheriton Urban District.	
	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.
1893	—	5	—	4	—	—	1	1		
1894	2	7	—	1	—	3	1	3		
1895	—	10	1	2	1	3	3	4		
1896	4	18	1	1	1	1	1	5		
1897	4	40	—	3	—	1	1	1		
1898	8	36	1	3	—	—	—	2		
1899	16	87	—	—	—	1	—	2	—	—
1900	5	50	—	—	1	9	—	1	—	—
1901	3	14	1	2	—	2	—	1	—	1
1902	6	26	—	2	—	2	1	2	1	3
1903	2	16	—	1	—	—	1	1	1	—
1904	1	7	—	3	—	2	—	2	—	—
1905	—	6	—	—	—	—	—	—	—	—
1906	—	11	—	2	—	—	—	1	1	1
1907	1	20	—	—	—	—	—	1	—	—
1908	—	9	—	—	—	—	1	3	—	—
1909	1	19	—	1	—	—	1	2	—	—
Total	53	381	4	25	3	24	11	32	3	5

Table showing the Incidence of Enteric Fever as regards the Age and Sex of Persons attacked during the Period 1896 to 1909.

Year.	−5	−15	−25	−35	−45	+45	Total at all Ages.	Males.	Females.	Over Age 15.	
										Males.	Females.
1896 ..	2	8	4	3	1	—	18	3	15	2	6
1897 ..	2	13	15	8	—	2	40	13	27	6	19
1898 ..	3	10	9	10	2	2	36	18	18	11	12
1899 ..	2	22	28	18	12	5	87	38	49	25	38
1900 ..	—	15	24	6	5	—	50	16	34	10	25
1901 ..	1	3	5	3	1	1	14	5	9	3	7
1902 ..	1	3	10	7	2	2	25	12	13	10	11
1903 ..	1	7	3	2	2	1	16	8	8	3	5
1904 ..	—	2	2	2	1	—	7	4	3	3	2
1905 ..	—	1	2	1	1	1	6	3	3	2	3
1906 ..	—	1	2	6	—	2	11	9	2	8	2
1907 ..	2	5	5	4	—	4	20	6	14	3	10
1908 ..	—	3	4	2	—	—	9	5	4	3	3
1909 ..	1	11	—	2	2	2	18	9	9	4	2
Whole period	15	104	113	74	29	22	357	149	208	93	145

During the period 1901 to 1909 the local Inspector of Nuisances had made careful inquiries which seemed to indicate that the milker referred to by Dr. Thomson in his report of 1901 was connected in other years with milk-farms said to be associated with the dissemination of enteric fever. Samples of this man's excreta were now procured (fæces and urine) and submitted to bacteriological examination. The typhoid bacillus was isolated by the writer from the fæces on the five occasions on which samples were taken—viz., August 31, 1909; September 6, 1909; September 11, 1909; September 25, 1909; and October 19, 1909. The urine was always negative. This milker N. was therefore a typhoid carrier. He was a man of about sixty years of age, enjoying excellent health. To his knowledge he had never suffered from enteric fever, nor had his wife or any of his children while living with him. The only severe illness he was able to recall occurred about thirty years ago. At that time he had suffered from lassitude, lack of appetite, and general malaise; and though he was not bad enough to take to his bed, the illness had left a lively impression on him and his wife. Up to the age of twenty-six N. had been a sailor. He then took up farm work, but did not become a regular milker till April, 1893, when he came to a farm in the Elham Rural District, close to Folkestone. From that time till August, 1909, he was constantly employed as cowman and milker on various farms near Folkestone—viz.:

No. 1 farm, April, 1893, to October 11, 1895, in Elham Rural District.

No. 2 farm, October 11, 1895, to October 11, 1896, in Elham Rural District.

No. 3 farm, October 11, 1896, to October 11, 1898, in Dover Rural District.

No. 4 farm, October 11, 1898, to October 11, 1902, in Elham Rural District.

No. 5 farm, October 11, 1902, to October 11, 1909, in Elham Rural District.

During N.'s stay at No. 1 farm there were five cases of enteric fever at the farm—viz., son and daughter of the farmer, a visitor, a maid-servant, and a charwoman.

At No. 2 farm there was one case of enteric fever while N. worked there.

At No. 4 farm two of the farmer's daughters had enteric fever while N. worked there.

TABLE SHOWING YEAR BY YEAR THE NUMBER OF CASES OF ENTERIC FEVER NOTIFIED IN THE URBAN DISTRICTS OF FOLKESTONE, HYTHE, SANDGATE, AND THE RURAL DISTRICT OF ELHAM, DURING THE PERIOD 1893 TO 1909.

In separate columns are shown the number of persons who contracted the fever outside the district (imported cases), and the number of persons who lived in houses deriving their milk-supply wholly or in part from a farm on which N. worked as a milker at the time of infection (N. cases).

	Folkestone Urban District.			Hythe Urban District.			Sandgate Urban District.			Elham Rural District.		
	Total Cases.	Imported Cases.	N. Cases.	Total Cases.	Imported Cases.	N. Cases.	Total Cases.	Imported Cases.	N. Cases.	Total Cases.	Imported Cases.	N. Cases.
1893	5	—	—	4	—	—	—	—	—	1	—	1
1894	7	—	—	1	—	—	3	—	—	3	—	3
1895	10	—	—	2	—	—	3	—	3	4	2	1
1896	18	1	13	1	—	1	1	—	—	5	—	3
1897	40	3	20	3	1	—	1	—	—	1	—	1
1898	36	1	14	3	2	—	—	—	—	2	1	—
1899	87	2	66	—	—	—	1	—	—	2	—	2
1900	50	5	38	—	—	—	9	—	—	1	—	—
1901	14	3	10	2	—	2	2	—	—	1	—	—
1902	26	4	15	2	1	1	2	—	—	2	—	—
1903	16	5	7	1	—	—	—	—	—	1	—	—
1904	7	—	4	3	2	—	2	—	—	2	—	1
1905	6	1	—	—	—	—	—	—	—	—	—	—
1906	11	2	1	2	—	—	—	—	—	1	—	1
1907	20	6	3	—	—	—	—	—	—	1	1	—
1908	9	2	3	—	—	—	—	—	—	3	—	2
1909	19	1	13	1	—	—	—	—	—	1	—	1
Total	381	36	207	25	6	4	24	—	3	31	4	16

For particulars with regard to the milk-supply in the various years and the enteric outbreaks associated with it, the original report must be consulted.

In the fourteen-year period 1896 to 1909, 359 cases of enteric fever are known to have occurred in Folkestone Urban District, and of these 36 are known to have been imported cases. Of the remaining 323 cases, 207, or 64 per cent., are known to have had milk, within three or four weeks preceding their illness, from one or other of the farms on which N. was at the time acting as milker.

Interesting data were obtained relative to the incidence of enteric fever as regards the age and sex of the persons who had taken N.'s milk, and in the following table the figures are set forth :

	−5.	−15.	−25.	−35.	−45.	+45.	Total.	Males.	Females.	Over 15.	
										Males.	Females.
1896	1	6	4	2	—	—	13	3	10	1	5
1897	—	8	7	5	—	—	20	7	13	3	9
1898	—	7	4	3	—	—	14	6	8	2	5
1899	3	17	18	13	10	5	66	20	46	16	30
1900	—	14	16	6	2	—	38	11	27	5	19
1901	1	3	3	2	—	1	10	3	7	1	5
1902	1	2	5	2	4	1	15	9	6	7	5
1903	—	3	1	1	1	1	7	3	4	1	3
1904	—	—	2	2	—	—	4	2	2	2	2
1905	—	—	—	—	—	—	—	—	—	—	—
1906	—	—	1	—	—	—	1	1	—	1	—
1907	—	1	2	—	—	—	3	—	3	—	2
1908	—	2	—	1	—	—	3	2	1	1	—
1909	1	8	—	1	1	1	12	4	8	2	1
Total	7	71	63	38	18	9	206	71	135	42	86

A comparison of these figures with those relative to the cases which had not taken N.'s milk revealed fairly clearly that there was a disproportionate incidence of enteric fever on females and children in the group which had partaken of N.'s milk. This undue proportional incidence is in itself suggestive of milk-borne infection.

To sum up: N., a typhoid carrier, worked at five different milk-farms as cowman and milker during the period 1893 to 1909. Enteric fever broke out at three of these farms during his stay there, and cases of enteric fever also occurred in the neighbourhood of all five of them. On the milk-round of each of the five farms there was undue prevalence of the fever at intervals during the time N. worked there, and no such prevalence was observed either before his advent or after his departure. During the period 1896 to 1909, 64 per cent. of the cases of enteric fever infected in Folkestone had been supplied with milk from a farm on which N. was working. Certainly milk from N.'s farm was supplied in two other districts for three months in 1901 without any known increase of enteric fever in these districts, and no cases of the fever could be attributed to N.'s milk during the year 1905; but, as Johnstone remarks, N. may have been only intermittently infective, and even had his condition been one of continuous infection, it was not inevitable that the infection should always reach the milk-supply. "On the whole facts it may be concluded that for the past fourteen years enteric fever has been spread in Folkestone Urban District mainly by milk, and that the milk was infected by N., a typhoid carrier."

The writer has been informed (March, 1912) that in 1910 there were only five notified cases of enteric fever in the Folkestone Urban District, and three of these were imported cases.

One of the most instructive milk-spread epidemics due to carrier infection is that reported by Scheller (1908).

For fourteen years (1894 to 1907) enteric fever had been prevalent on an estate in the neighbourhood of Königsberg. Thirty-two persons had been certainly infected, but there may have been many more who had slight attacks only. The people affected had all to do with the estate, and there were no cases notified in the village adjoining the estate. The evidence did not point to the water-supply as the source of infection, and measures of house disinfection were fruitless in stemming the outbreaks. An extensive investigation was then undertaken from the carrier point of view.

Eight of the 32 persons attacked had their own cow, while 23 others received their milk regularly from the estate. In one case it was no longer possible to ascertain whether the family concerned had possessed a cow of their own or not. The total number of people who were supplied with milk from the estate was about 40, while the number who possessed their own cow was 140. With regard to the 8 cases of this latter series, it was ascertained that, though they had their own cows, they applied for milk to the estate when the cows went "dry." The presumption was therefore strong that some relationship would be found between the milk-supply from the estate and the cases of enteric fever. The milk that was not consumed on the spot was not sold, but was employed for the feeding of swine. Only the butter was sold to certain people, and amongst these no cases of typhoid fever occurred. It was thus explained why the epidemic remained a local one.

The personnel of the dairy was then inquired into. One woman, Frau U., was found to have had typhoid fever seventeen years previously. She had been engaged on the estate for about thirty years. From the estate books it was ascertained that she had commenced dairy work fourteen years before, and just a short time before the occurrence of the first case of typhoid fever. Her stools contained typhoid bacilli practically in pure culture, and they were occasionally demonstrable in the urine.

Bacteriological investigation was then made of the excreta of the 40 persons who consumed the milk from the estate, or who assisted in any capacity in the dairy work. Of these 40 persons no fewer than 18 were found to be carriers. One was the woman above mentioned. Of the others, four had had enteric some considerable time previously, while in the remaining 13 no record of a previous attack could be ascertained. The 4 carriers who had had enteric fever previously could have played no part in spreading the infection by milk, as they had never had anything to do with its preparation.

A large proportion of the 140 persons who received no milk from the estate was also examined, but with negative results.

The point to be determined now was whether the woman already mentioned was a geniune chronic carrier and whether the other 17 carriers were also to be classed as such.

It may be noted here that these 17 persons were examined on three occasions at intervals of twelve days. Four were found to be passing typhoid bacilli both in the stools and in the urine, 7 in the stools only and 6 in the urine only. The following test was made : Frau U. was discharged from her dairy work, and all the other carriers who were engaged in the milk business were strictly enjoined to wash their hands in lysol before milking. Further, the milk that was not used for butter was boiled before distribution. The urinary carriers also received urotropin. After a month under this régime all the carriers were again examined, when it was found that Frau U. was still discharging bacilli in large numbers, while repeated examination of the others (at fifteen-day intervals) gave negative results. From this it was inferred that Frau U. was a genuine chronic carrier, while the other 17 were only temporary carriers.

Scheller believed, on grounds which in the light of more recent knowledge appear insufficient, that he had discovered a type of carrier in which the typhoid bacilli lead a true saprophytic existence in the intestinal canal, and cause no disturbance whatever in the organism of the host.

Lentz had previously held the views (1) that a large proportion of these transitory carriers had really reacted to the presence of the typhoid bacilli by slight and possibly unnoticed symptoms, and (2) that those who did not have symptoms even of the slightest order were still to be classed as "symptomless" typhoid cases, in view of the fact that the agglutinin reaction in such cases rose to the same titre as in clinically typical enteric cases. With this latter statement of Lentz, Scheller does not agree, as he had noted the absence of agglutinin reaction in some of these cases, while in others he had undoubtedly observed as high a titre as 1 in 2,000. The 17 temporary carriers who ceased to carry, as already described, Scheller preferred to classify in a new group of *Typhusbazillenzwischenträger* (intermediate carriers).

The view is open to criticism for the following reasons: In the first place, 4 of these 17 carriers had had a definite primary infection, and the actual number of examinations was only three during a period of one month. Without further evidence, therefore, these 4 persons would not properly be classed as temporary carriers.

In the second place, with regard to the remaining 13 who had never had the slightest symptoms of typhoid fever, one would wish to know whether any of them developed the disease at a later period, as the possibility of a prolonged incubation stage is now well recognized. It is not disputed that this purely saprophytic growth may in some cases take place, but much fuller evidence is demanded before we can admit that such cases have never at any time exhibited symptoms either clinical or serological.

Stott (1910) gives a most interesting account of enteric fever prevalence in a hamlet in Mid-Sussex, which he traced to milk polluted by a carrier in the person of a milkman. It is impossible here to give more than a summary of the chief features. From 1899 to 1910 (July) 58 cases of enteric were notified in the hamlet, the cases being distributed thus:

1899	4 cases in	3 houses.
1900	3 ,,	1 ,,
1901	4 ,,	3 ,,
1902	5 ,,	2 ,,
1903	7 ,,	6 ,,
1904	6 ,,	4 ,,
1905	No cases.	
1906	,,	
1907	1 case in gipsy van.	
1908	No cases.	
1909	19 cases in	12 houses.
1910	9 ,,	9 ,,

The milk-supply of the hamlet was derived from nine separate dairymen, but inquiry elicited the fact that all the affected houses obtained their milk-supply from a dairy farm on which a certain person, F., milked the cows, and also carried the milk round the district. The cases of 1899 had their milk from this milk-seller, X., whose two children were also ill in November of that year. The three cases of 1900 also had their milk from X. The four cases of 1901 occurred at a large house with an independent milk-supply, but the milker was the man F., who had left the service of X. in the interval. The cases of 1902 occurred again in the house of X. Before that time F. had left the large house and returned to the service of X. as milkman. The 1903 cases had their milk from X., so also the cases of 1904. In 1905, 1906, and 1908, no cases were notified in the district. The single case in 1907 was a gipsy caravan-dweller. During this period of immunity from enteric fever F. was not employed as milkman, but was doing odd jobs. The nineteen cases in 1909 had their milk from a farmer who had employed F. as milkman. "As soon as F. was engaged as cowman, enteric fever seems to have appeared." F. was suspected of being a carrier at this time, but, unfortunately, the urine only was examined, and was returned as negative. He was accordingly at this time acquitted.

In 1910 further cases arose, which also had their milk-supply from the farm on which F. worked.

Samples of fæces were now obtained from F. and examined by the writer, and he was proved to be a carrier. Examinations of excreta of other persons on the farm were negative. The carrier F. was born in 1860, and had lived about the district all his life. In 1893 he contracted enteric fever. From infancy he had suffered from facial paralysis, and had no control over his flow of saliva. No typhoid bacilli, however, were found in the saliva. Since F. was declared to be a carrier, he has not been engaged in dairy work, and I am informed by Dr. Stott (1912) that since July, 1910, no cases of enteric fever have occurred in the district. His fæces continue to harbour typhoid bacilli (May, 1912).

In the present year (1912) cases of milk-borne typhoid infection have been traced to carriers by Bolduan and Noble (1912) in the case of a New York outbreak, and by Carnwath (1912) in the Urban District of Willington, in the County of Durham. Space will not permit of my referring to these in detail. Both reports afford very convincing evidence of the infectivity of the carrier who has to handle milk.

Institutional Cases.

A large proportion of typhoid carriers have been found in institutions like asylums, workhouses, private schools, etc., where typhoid fever has been of endemic occurrence. In such establishments the intimate contact prevailing among the inmates must play a large part in facilitating the spread of infection from case to case. In lunatic asylums especially, the filthy personal habits of many insane people are naturally accentuating factors where a carrier or carriers are already in existence. Some attempts have been made to explain the presence of large numbers of carriers in lunatic asylums, and the hypothesis has been put forward that a psychosis is a predisposing factor to the carrying status.

There is no evidence in support of this view, but there is much to be said for the view held by some observers, that the proportion of carriers discovered in institutions may ultimately prove not to be unduly large, since the facilities for thoroughly carrying out bacteriological investigations on a large scale are greater than is usually the case elsewhere, and correspondingly increase the probability of detecting the presence of carriers.

Several striking instances of endemic typhoid fever in asylums have been recorded in recent years. To a few of these only reference will be made.

In 1908 A. and J. C. G. Ledingham recorded the results of an investigation into the cause of recurring enteric fever in a lunatic asylum in Scotland. This asylum in 1908 contained 92 male and 53 female patients, 8 male and 6 female attendants, and 4 female servants. Since 1893 there had been a succession of small outbreaks of typhoid fever in this asylum, the female inmates being principally affected. Also similar outbreaks had occurred periodically in a smaller detached building containing 32 female patients, and situated about five minutes' walk from the main building. Prior to the adoption of the Notification Act in 1891, no authentic records of typhoid fever in this asylum were available. The table on p. 52 shows the incidence of typhoid fever in sucessive years since 1893, when the first case was notified.

It will be seen that 31 cases in all occurred, and 24 of these were females—viz., 21 female patients, 3 female attendants, 6 male patients, and 1 male attendant. Nine of the cases proved fatal. The cases arose at no special season of the year, but in individual years the notifications followed each others as a rule very closely. During 1894, 1898, 1902, and 1905, no cases were notified.

The mysterious cropping up of typhoid cases had been a source of great anxiety to the authorities, who had done everything in their power to make the sanitary arrangements of the institution as complete as possible. Repeated analyses of the water-supply, both chemically and bacteriologically, threw no light on the etiology of the outbreaks. The sewage was conveyed direct to the sea, and the dairy arrangements were in excellent order. The same water-supply served several families residing on a farm near the source of the supply, but at no time had cases of enteric fever occurred among them. It was accordingly determined to search for carriers among the inmates. In February, 1907, a start was made by testing the Widal reaction in a group of 43 female patients, and 6 of these, 2 of whom had had enteric fever previously (in 1903 and 1904 respectively), gave a well-marked reaction. In the course of this work, however, A. L. contracted a severe attack of typhoid fever, and nothing further was done in the matter till September, 1907, when it was proposed to examine bacteriologically the stools of all the female patients in the asylum. Three female typhoid carriers were thus discovered. The first, G., had been in the asylum (main block) since 1896. She was thirty-five years of age, and there was no record of a primary infection.

Year.	Total No. of Cases.	Month of Notification	Main Asylum.	Small Asylum.
1893 ..	2	March, July	2	—
1894 ..	—		—	—
1895 ..	6	July (2), August (3), December (1)	1	5
1896 ..	2	April, May	2	—
1897 ..	1	November	—	1
1898 ..	—		—	—
1899 ..	4	August (1), November (3)	4	—
1900 ..	3	January, June, August	1	2
1901 ..	2	February, May	2	—
1902 ..	—		—	—
1903 ..	4	February, March, April, October	4	—
1904 ..	3	June, July, August	3	—
1905 ..	—		—	—
1906 ..	1	April	1	—
1907 ..	3	February, April, October	2	1
Total ..	31		22	9

Her personal habits were exceedingly filthy. She had not, however, been employed either in the laundry or kitchen. Her serum gave a Widal reaction in a dilution of 1 in 200.

The second carrier, McC., had been in the small detached building since 1895, when she had had an attack of typhoid fever. She was about sixty years of age, and was able to walk about and do a little work, but had never been employed in the kitchen. Her habits were cleanly, and occasionally she had assisted in the laundry. Her serum gave a Widal reaction in 1 in 200. It has to be noted that, though there are two separate blocks, much communication goes on between them. The dinners are cooked at the main block, and brought over to the smaller block; the clothes are washed also at the main block, but patients from the small block would sometimes assist.

The third female carrier, C., was about thirty years old, and had typhoid fever in 1904. She was not of dirty habits, but had never been employed in the kitchen or laundry. Her serum gave a marked Widal reaction.

These three females were isolated as soon as they were discovered to be carriers, and since November, 1907, they have remained in the isolation block with a special attendant.

Since October, 1907, up to the present date (April, 1912), the asylum has enjoyed complete immunity from typhoid fever. The fæces of these three isolated carriers were examined by the writer in March, 1912, and in two of them typhoid bacilli were present in considerable numbers.

The female carrier case reported by Davies and Walker Hall (1908) is so well known in this country that I need only refer to the most important features of the outbreaks for which she was responsible. In November, 1906, an outbreak of typhoid fever occurred in an inebriate reformatory near Bristol. This institution then contained 240 inmates and 24 resident officers. There had been no visitation of typhoid fever since the opening of the institution in 1899. No cases of typhoid fever existed in the neighbourhood at the time of the outbreak. In September, 1906, a kitchen helper took ill, and in November three more cases occurred in which the suggestion was that the infection was conveyed by milk. One was a female inmate who received an extra allowance of milk daily, as she was nursing; another was the gardener's wife, who lived in a detached cottage and received only milk from the institution. The third was an out-door policeman who received an allowance of milk for his tea. No explanation of the initial case was forthcoming. Fresh outbreaks occurred in May, 1907, and continued up to November—viz., May, 1 case ; June, nil ; July, 6 cases ; August, 9 cases ; September, 1 case ; October, 2 cases ; November, 4 cases—*i.e.*, 23 cases altogether.

The evidence in the 1907 cases was still stronger against the milk, which evidently had some opportunity of being contaminated after sterilization. It was learned that an inmate, Mrs. H. (fifty years), employed as cook and dairymaid in the institution, had suffered in January, 1901, from typhoid fever. She had been admitted to the reformatory in April, 1906, and was employed in kitchen work up to October 13, 1906, when she was entrusted also with the dairy work, which she continued up to November, 1907. At Dr. Davies's suggestion, she was excluded from kitchen and dairy work on November 13, and twelve days afterwards, November 25, the last case of the series occurred. On November 18, 1907, her serum gave a negative Widal reaction, and the stools and urine were typhoid-free. On November 29, 1907, the stools also proved negative, but a positive result was obtained on December 20, 1907. Further examinations on January 20, February 14, February 18, and March 14, were, however, negative. The urine was always negative. The fæces again proved positive on April 14, 1908. (For further data on the bacteriological examinations of the excreta of this case see p. 115.) The milk after sterilization was stored in the dairy, whence it was measured out for the various blocks by means of a hand-dipper. All the milk passed through her hands. It is evident, therefore, that the milk which was shown to have been the agency by which the fever was disseminated could readily have been infected by Mrs. H.

Inquiry into the past history of this carrier showed that she had been, in all probability, responsible for enteric outbreaks in at least two other institutions.

In May, 1904, typhoid fever broke out in the Grove House Home for Girls at Brislington, near Bristol. This institution was then occupied by 36 girls (five to fifteen years), who were boarded out by the Bristol Guardians. From May to the end of September, 26 persons in the institution developed enteric fever. Eight suspicious cases also occurred. Two cases ended fatally.

There had been no typhoid fever in the district for months, and the sanitary arrangements of the institution could not be impugned. All attempts to combat the spread of the disease by disinfection, boiling of milk, etc., were fruitless. It appears that Mrs. H. had on February 3, 1904, been transferred from the Bristol Workhouse to the kitchen at Grove House, Brislington. Her duties were to assist in the kitchen and to cook, and all the milk, which was boiled, passed through her hands. It is notable that she left Grove House Home on September 2 to take a private situation, and the last case in the institution was notified twenty days later—viz., on September 22, 1904.

It was further ascertained that on March 4, 1905, this carrier became cook at a children's home where there were 30 girls. Nothing happened till May 8, 1905, when one of the girls developed enteric fever for which no cause could be found. The cook had left at the end of April. No further cases occurred.

During the past eighteen months, since the writer's report appeared, the question of the part played by carriers in maintaining the endemicity of enteric fever in asylums and similar institutions has been investigated in not a few cases. The features are very similar in all, and it would appear unnecessary to refer to them in detail. The reader may with profit consult the reports of Eccard (1910) on the Frankenthal Asylum in the Pfalz district, of Zweig (1910) on the Dalldorf Asylum, of Ast (1911) on the Eglfing Asylum, of Günther and Böttcher (1911) on the Imperial Saxon Landesanstalt at Hubertusburg, and of Bernhuber (1912) on a residential school. Points in connection with these cases will be referred to in later sections, but it may be of interest to refer in some detail to Brückner's (1911) description of an outbreak in an academy for boys, as the investigation brought to light some features which have not been observed in institutions containing mainly adult persons.

The academy contained 102 boys of ages six to fourteen. In 1910 the following cases occurred in the institution :

End of January	1 boy (convalescent March 2).
April 27	1 boy.
End of May	2 boys and 1 governess.
End of June	1 governess.
Beginning of July	1 boy.
End of July	1 boy.

There was then a pause of thirty-two days, when no fewer than 67 cases occurred in the period from September 1 to 10 None of the cases proved fatal ; in fact, so slight were the symptoms in many instances that, had there not been definite cases earlier in the year, and a large proportion of the boys now ailing, the typhoidal nature of the outbreak might have been overlooked. No connection could be traced between the first case and those that occurred three months later, and it was held to be imported.

On May 25 typhoid bacilli were got in the fæces and urine of a kitchenmaid who had arrived in the middle of March, and who shortly before (in February) had passed through a typhoid-like infection. A Widal reaction was still obtainable on June 3. She left the institution in the middle of July, and the problem was how to explain the September cases. Brückner, who has on several occasions laid stress on the atypical course of enteric fever in children, had no difficulty in coming to the conclusion that the spread in September was really a contact one, and that the early September cases had contracted the disease in August. The only evidence of enteric fever in the majority of the cases was a rise of temperature and the presence of a Widal reaction. Many of the children found to be infected had been playing about all the time. Of the 67 cases notified as enteric, 29 had the bacilli in the blood, stools, and urine. The extraordinary mildness of the fever in these cases led Brückner to classify three forms in which enteric fever may occur.

First Type.—Transitory saprophytic typhoid infection, in which the bacilli occasionally traverse the intestine without giving rise to any symptoms. Bacilli can be demonstrated in the stools, and a slight Widal reaction is obtainable. This corresponds to the so-called "symptomless typhoid fever of Lentz." The term "saprophytic," however, is probably not justified, as the bacilli at least make their presence known by stimulating the body cells to antibody production, which a true saprophytic organism, such as *Bacillus coli* in the intestinal tract, is unable to do. It is highly probable that even in these cases the typhoid bacillus has a transient sojourn in the blood-stream.

Second Type : Abortive Typhoid.—In this condition there is a subfebrile temperature, a marked Widal reaction, and bacilli are demonstrable in the fæces, and perhaps in the blood.

Third Type : Genuine Enteric Fever with Septicæmia.—The morbidity is, in Brückner's view, probably higher in children than in adults, and certainly not less.

As I have mentioned, the higher frequency of carriers in asylums as compared with that found in the neighbourhood of typhoid cases elsewhere has been attributed by some to a psychosis predisposing typhoid-sick lunatics to this condition.

There are, however, certain considerations which tend to discountenance the need for adopting such an explanatory hypothesis as this. In the first place, much greater facilities are afforded to one chronic carrier, of unclean habits, of infecting her associates, who may then act as temporary carriers or who may become chronic carriers. In the second place, as Eccard suggests, a lunatic typhoid convalescent of filthy habits is probably always reinfecting herself, and so develops into the chronic type. This view has been applied in a wider sense to all chronic carriers by Fornet, who, as I have said, maintains that the carrier state arises from a symptomless reinfection.

Army Carriers.

The association of carriers with occurrences of typhoid fever in army barracks, etc., presents features similar to those met with in civil communities, and it will suffice to describe two striking instances out of a considerable number now on record.

The first of these occurred in an artillery barrack at Wesel. During the period 1904 to 1908 this barracks had been, according to Niepratschk (1909), who reports the case, a "veritable typhoid house." Its hygienic conditions were excellent, and no source of infection could be traced. Since October, 1902, it had been occupied by the artillery regiment, and on January, 1904, the first case of typhoid fever occurred. During the five years 1904 to 1908 there had been 31 cases of typhoid fever, of which 6 ended fatally and 4 led to invalidity. The cases occurred as follows :

1904	..	1	case (January).
1905	..	7	cases (February, May, October [3], November, December).
1906	..	2	,, (April and October).
1907	..	20	,, (10 between January and June ; 10 between September and November).
1908	..	1	case (February).

The first two cases were attributed to infection contracted during Christmas leave, and the third case was also in all probability imported. For the other cases no probable source of infection was forthcoming. Neither in the civil population nor in the other troops of the garrison was the typhoid incidence high. The opinion that water played any part in the spread of the fever had to be abandoned after careful attention paid to the water-supply had yielded no result. The hypothesis that a carrier might be at the root of the trouble was then tested, and a commencement was made with an examination of the fæces and urine of the lessee and assistants in the canteen. The cook (a female of fifty-five years of age) had had enteric fever two years before, and in August, 1907, had suffered from a febrile attack pointing to gall-bladder trouble. Repeated examinations of her fæces and urine were, however, negative, and she gave an absolutely negative Widal reaction. The examinations of the stools and urine of all the other assistants were negative.

Then began a systematic examination of the *Unteroffizieren* of the individual batteries. On February 23, 1908, Sergeant B. was found to be excreting large numbers of typhoid bacilli in his urine. No other carriers were found.

The history of this man was as follows : In the spring of 1901 (March 5 to April 29) he had had a severe attack of enteric fever while serving in a regiment of dragoons at Tilsit. His urine during the fever had been free from albumin. On April 29 he was sent home to recruit, but eight days later he had a severe relapse, and for eight weeks could not be transported. On June 20 he returned to the regimental hospital, and remained there till July 8. At the close of his three years' service in October, 1901, he spent a year at home. On October 1, 1902, he joined the 15th Ulan Regiment at Saarburg, where he remained till October 1, 1903. He then returned home, but enlisted again on June, 1904, in the 1st *Trainbataillon*, at Königsberg. With this regiment he remained only one year, and on June 15, 1905, joined the artillery regiment at Wesel.

Some suggestive facts were later ascertained with regard to typhoid outbreaks in other regiments to which this man belonged before coming to the Wesel garrison. Thus, in the year in which Sergeant B. was in a *Trainbataillon* one case occurred, while during the previous three years there had been no cases in that regiment. Also during his service in a Ulan regiment, fifteen cases had occurred in 1903. None had occurred before his arrival, and none after his departure.

Sergeant B. was a robust, healthy man of thirty-one. His urine was slightly acid, showed slight cloudiness, but contained no albumin. Cellular elements were not present. It was calculated that the urine contained 2,500,000 of typhoid bacilli per c.c. The strain was markedly avirulent for guinea-pigs, a fact which was in striking contrast with the severity of infections caused by it. When first isolated it would not kill guinea-pigs of 250 grammes weight in doses under a quarter of a whole agar culture. By passage, however, the lethal dose was lowered to one quarter of a loop. B.'s serum gave an incomplete Widal reaction (1 in 50 positive in two hours, 1 in 100 negative in two hours, at 37° C.), and the bactericidal power of the serum was also very low. The fact that the virulence could be raised by passage through the guinea-pig suggested to Niepratschk that a similar process might take place by passage through human beings. Thus, cases with only slight symptoms might give rise to infections of a severer type. There was the further possibility that the strain might undergo temporary alterations in virulence. In Niepratschk's view, however, one thing was certain—viz., that since October, 1905, the typhoid outbreaks in the artillery barracks could be traced only to this carrier. Among the other troops in Wesel and in the civil community there had been only a few cases.

In the following table are given the figures of typhoid incidence in the artillery department compared with that in other garrisons at Wesel and in the civil population :

Typhoid Incidence per 1,000.

	1904.	1905.	1906.	1907.	1908.
Affected artillery detachment	2·74	19·18	5·48	54·79	2·74
Other garrisons	—	1·07	0·53	0·26	—
Civil population	0·36	1·18	0·20	0·61	0·10

The table shows very clearly the heavy incidence of typhoid fever in the artillery detachment.

All three batteries of artillery were equally affected (1st Battery, 11 cases ; 2nd Battery, 9 cases ; 3rd Battery, 11 cases), and not Sergeant's B.'s battery only. B. stated that he was in the habit of passing his urine only in the latrine. He may, however, in Niepratschk's opinion, have urinated occasionally in the stables, so that the persons who had to change the straw or clean the stalls may readily have soiled their fingers or the soles of their boots with the typhoid bacilli. When they came to clean their boots the same danger was present. It was significant that the shoemaker who mended Sergeant B.'s boots took typhoid fever. Out of the twenty-eight cases, only two *Unteroffizieren* (the class to which Sergeant B. belonged) developed typhoid fever, and it is suggested that their immunity arose from the fact that they did not brush their own boots.

Sergeant B. was isolated for two years, and no further cases occurred in the regiment. The treatment adopted with apparent success in the case of Sergeant B. will be referred to in the section on urinary carriers.

The second instance of carrier infection in army units to which I shall allude occurred in the barracks at Kilworth (Ireland) in 1909. According to the report by Dorgan (1910), twenty-four cases in all occurred among the various regiments stationed at Kilworth during the period May to August, 1909, and the following table shows the dates of onset, with remarks relative to the origin of the milk supplied to the respective messes affected :

No.	Name.	Regiment.	Onset.	Remarks.
1	Capt. C. ..	E. Yorks.	24.5.09	Inspector of musketry. Had tea in garrison mess about end of April.
2	Lieut. D. ..	Sherwoods	8.7.09	Lived at garrison mess. O'N.'s milk.
3	Pte. R. ..	,,	17.7.09	Waiter at garrison mess. O'N.'s milk.
4	Lieut. P. ..	S. Lancs.	12.7.09	Officers at a detached mess, and used O'N.'s milk. Privates acted as waiters.
5	Lieut. M. ..	,,	17.7.09	
6	Pte. C. ..	,,	15.7.09	
7	Pte. A. ..	,,	17.7.09	Died.
8	Capt. B. ..	R.M.F.	26.8.09	Regimental mess. O'N.'s milk.
9	Lieut. H. ..	R.A.M.C.	23.8.09	Garrison mess. O'N.'s milk.
10	Lieut. W. ..	R.W.F.	24.8.09	
11	Lieut. M. ..	R.M.F.	28.8.09	Regimental mess. O'N.'s milk.
12	Lieut. D. ..	,,	31.8.09	
13	Lieut. S. ..	,,	1.9.09	
14	Lieut. H. ..	,,	31.8.09	
15	Lieut. E. ..	,,	1.9.09	
16	Lieut. C. ..	,,	30.8.09	
17	Capt. S. ..	,,	3.9.09	
18	Pte. D. ..	,,	16.8.09	Kitchen man (officers' mess). Had been ill a few days on duty, and may have infected the mess.
19	Pte. J. ..	,,	2.9.09	Mess waiter.
20	Pte. S. ..	,,	30.8.09	Regimental duty ; the only case that cannot be traced to the milk.
21	Lce.-Serg. S.	,,	23.8.09	Died.
22	Serg. B. ..	,,	21.8.09	Sergeants' mess. O'N.'s milk.
23	Pte. G. ..	Conn. Rang.	27.8.09	Mess waiter. Admits drinking unboiled milk.
24	Child " B."	R.E.	19.8.09	Visited camp and drank milk at O'N.'s farm on August 10.

In all cases the milk, which, contrary to explicit regimental orders, appeared to have been consumed in the unboiled state by the soldiers attacked, came from the same farm occupied by a farmer O'N. The members of O'N.'s household were examined by the Widal test, and one girl, a dairymaid, was found to give a definite reaction in 1 in 100. After some difficulty, specimens of her excreta were obtained, and the *B. typhosus* was isolated from her urine. This woman had had enteric fever in 1903, when she was employed at this farm. Six months after her attack she returned to her duties there, when the farmer and his child were attacked. In 1906 she was employed in a similar capacity by a farmer at "G," near Kilworth. Soon after her arrival the farmer's child became ill, then the farmer himself and his wife, and also a labourer's wife and child. Two other children who had been at a boarding-school returned home on vacation, and both developed typhoid fever. On February 1, 1909, she returned to reside at O'N.'s farm, but since November, 1908, she had worked there at odd times. Two sisters of O'N. died in December, 1908, of an acute fever which was subsequently believed to have been enteric. Also a carpenter working in the camp and drinking O'N.'s milk contracted typhoid fever on February 7, 1909. It was further ascertained that another married sister of O'N., who lived on a farm about a mile away, was ill with enteric fever in September, 1909. There was much communication between the two houses. Also in the same month a civilian post-office clerk contracted typhoid fever. O'N. supplied this post-office with milk.

Including the civilian cases, this urinary carrier appears to have been responsible for about forty cases of typhoid fever altogether. For an excellent account of the bacteriological work carried out in connection with this case, the reader may be referred to Professor McWeeney's report to the Local Government Board for Ireland (1910).

PATHOGENESIS OF THE TYPHOID-CARRYING STATE, WITH PARTICULAR REFERENCE TO THE INTESTINAL CARRIER.

The discovery of the typhoid bacillus in cases of cholecystitis, cholelithiasis, bone abscesses, etc., long after recovery from the primary infection, was made many years previously to the recognition of the typhoid carrier. The fact also that, at post-mortem examinations of persons who have died of typhoid fever, the typhoid bacillus is invariably found in the bile and in the upper portion of the small intestine has been known since the work of Anton and Fütterer (1888), and later of Chiari (1894) and many others. In 1899 Droba recorded a case of cholelithiasis which came to operation, in which the *B. typhosus* was isolated from the gall-bladder contents, as also from the interior of the gall-stone. The interval since the primary typhoid infection was seventeen years.

Similar finds of the *B. typhosus* in cases of cholelithiasis at longer or shorter periods after typhoid fever were made by Miller (1898), Brion (1901), Findlay and Buchanan (1906), Simon (1907), Dudgeon (1908), and many other observers.

A definite history of a typhoid infection in these cases may be wanting. Thus, Blumenthal (1904) records two cases where there was no previous history pointing to typhoid or any like infection. One of these was a woman of thirty-seven years, who did not remember having had an attack of typhoid fever. At the operation the gall-bladder contained two round stones, the cystic duct and the choledochus were patent, and the typhoid bacillus was recovered from the pus in the gall-bladder, but not from the gall-stones. In this case the fæces and urine were examined and found negative. It must be remembered, however, that a single negative examination of the excreta can lead to no definite conclusion.

Though this person had never had typhoid fever, according to her own story, it was ascertained that her husband died of typhoid fever, that her brother and a child of her own (ten months old) suffered from a typhoidal attack in the beginning of January, 1904, while in a house only 100 yards distant there had been five cases of typhoid fever. It seemed therefore highly probable, in view of such evident association with typhoid cases, that she might have passed through an ambulant form of fever, culminating in cholelithiasis. Her serum agglutinated the homologous strain in the unusually high dilution of 1 in 2,500. Cushing's (1898) case also presented no history of enteric fever. The Widal reaction was positive, and typhoid bacilli were present in the bile.

The case reported by Findlay and Buchanan in 1906 presents points of great interest in connection with the carrier question, as it is one of the few cases in which examination of the fæces was carried out. A married female, aged fifty-one years, had suffered from weakness, loss of appetite, and a severe bilious attack, two months before seeking advice (August, 1905). In 1880 she had had a febrile attack lasting three weeks, which was thought to be gastric fever. On examination in August, 1905, a large painless tumour was found in the region of the gall-bladder. Her temperature reached 103·2° F., and during the first five days while she was under observation the temperature curve suggested that of a declining typhoid fever, but there were none of the classical signs of the disease. Her blood gave a positive Widal reaction (1 in 50 in an hour). A diagnosis of typhoidal cholecystitis was made, and was supported by the discovery of typhoid bacilli in the fæces. At the operation on August 15 the gall-bladder was found to be greatly distended, and a clear watery fluid escaped, followed by milky, and finally purulent, material. Drainage was resorted to, and from August 19 to September 22 typhoid bacilli were constantly present in the discharge. About thirty small stones were washed out at intervals. Bacteriological examination of the discharge on September 22 and 28 did not reveal the presence of the typhoid bacillus. On October 4 signs of pleural effusion, breathlessness, and abdominal distension, supervened, and death took place on October 14 as the result of cardiac failure. The pleural fluid was sterile. Unfortunately, no post-mortem examination was made in this case, but it seems highly probable, in the light of very similar cases reported of late, that this woman had been for many years a chronic carrier, and had succumbed to an auto-infection.

In a case reported by Dudgeon there was no history of typhoid fever. The patient had served in the army in India, and in 1900 had suffered from a severe attack of colic. No further attack took place until six months before coming to hospital (1908). Jaundice supervened, and his blood gave a reaction in a dilution of 1 in 500. An operation was performed, and a gall-stone was removed which was sterile, but the bile contained typhoid bacilli. The fæces and urine were negative. Three weeks later the bile still showed the *B. typhosus*.

An acute cholecystitis may, however, occur at a very early period of convalescence from typhoid fever. The case reported by Gilbert and Girode (1893) is of interest from the fact that a microscopical examination was made of the gall-bladder wall. The patient was a female of forty-five years, who developed a purulent cholecystitis in the fifth month of her convalescence from typhoid fever. On operation calculi were found, and the typhoid bacillus was present in the pus. Sections of the bladder wall showed accumulations of small cells in the mucosa, with masses of typhoid bacilli embedded in them. Hilgermann (1909) gives an account of a woman (aged twenty-nine years) who contracted typhoid fever on August 23, 1908, and whose temperature fell to normal on September 24. Shortly afterwards a sudden attack of gall-stone colic supervened, and in the course of ten days a tumour developed in the gall-bladder region. On October 4, 1908, the gall-bladder was extirpated. The fæces on October 16 were negative, but on October 20 typhoid bacilli were present. Later examinations, however, were negative, and she was discharged cured on November 20. The gall-bladder contained 300 c.c. of foul-smelling fluid and a stone of the size of a pea. From the pus the *B. typhosus* was recovered in pure culture. Histological examination of the gall-bladder wall showed disappearance of the epithelium and inflammatory infiltrates in the submucosa and muscularis. Typhoid-like bacilli were present only in the subserosa. In Hilgermann's view, the bacilli had penetrated from the inside of the gall-bladder through the epithelium into the deeper layers, and so to the outer wall. One might therefore readily conceive how, with a chronically inflamed mucosa and the presence of typhoid nests in the layers of the bladder wall, fresh infections of the gall-bladder contents might periodically occur, and so in some measure explain the intermittent excretion of bacilli by the fæces. The importance of a case like this lies in the fact that some light is thrown on the pathogenesis of the typhoidal cholecystitis, and all such observations are of value at the present time. As we shall see, a very similar condition of affairs has been found in fatal cases of enteric fever (Josef Koch, 1909), and experimentally in rabbits (Chiarolanza, 1909; Morgan, 1911). In the above case we noted that the fæces contained typhoid bacilli on the sixteenth day after operation, and thereafter were typhoid-free. In connection with treatment (*vide* p. 85), the value of cholecystectomy as a remedy for the carrier condition will be discussed; but it may be remarked here that, in order to be certain that the patient is bacteriologically typhoid-free, a much longer period of observation is necessary. The case, however, was a very early one in typhoid convalescence, and as such it seems quite possible that a bacteriological cure was effected before chronic changes in the gall-bladder and in the neighbouring parts had had time to establish themselves.

A case bearing on this point was observed by Theodore Thomson and the writer. Mrs. B. had enteric fever in June, 1909, and was discharged from hospital on July 2. The last two of the three examinations of her fæces before discharge were positive, but the urine was always negative. No further samples could be procured from her after her discharge. She commenced to suffer from gall-stone colic in October, and was admitted to St. Bartholomew's Hospital on November 1, 1909. The stools and urine were there examined, with negative results, on November 2. On November 19 she was operated on, when a small gall-bladder with thick walls and full of stones was removed. The contents of the gall-bladder contained typhoid bacilli, but the fæces and urine were negative.

Samples of this woman's stools and urine were examined by the writer on December 7, 1909, when the fæces were found to contain typhoid bacilli. She was discharged on December 15, 1909. Another examination of the fæces in February, 1910, was negative. It is of great importance that a case like this should be periodically examined, with a view to discovering whether a real cure has been effected. It has, however, proved impossible to obtain further samples of the woman's excreta.

Hertz and Adams (1910) have also reported a case in which a purulent cholecystitis accompanied by gall-stones intervened at an early period in convalescence from typhoid fever. The patient (female of twenty-four years) was admitted to the Brook Fever Hospital on December 22, 1909. Her temperature fell to normal on January 2, 1910, but a relapse occurred from January 14 to January 24. On February 1, 1910, she complained for the first time of pain in the epigastrium and back, accompanied by vomiting. The gall-bladder was found to be enlarged and tender. On February 18 the temperature rose to 99·4° F., and she was sent to Guy's Hospital, where she was operated on the same evening. The gall-bladder was opened, and after about 4 ounces of colourless clear fluid had escaped, about ½ ounce of pus was evacuated along with twenty-five faceted cholesterol gall-stones. The *B. typhosus* was recovered from the pus and from the centres of some of the gall-stones. The gall-bladder was drained, and the patient made a good recovery.

Since the discharge of this case from hospital the writer had an opportunity of examining her excreta on two occasions—viz., April 2, 1910, and May 13, 1910. On both occasions the fæces were found to contain typhoid bacilli, so that no improvement in the carrier condition could be recorded as the result of the operative procedures carried out. It has been impossible to obtain further samples.

Hitherto I have referred to the finding of the *B. typhosus* in persons suffering from cholelithiasis who had not previously been regarded as typhoid carriers in the sense in which the term is used in this memoir, but there can be little doubt that many of these cases would have been found to be actively or intermittently excreting the *B. typhosus* in the fæces had the attention of the bacteriologist or those concerned been directed to this possibility.

Before passing to the discussion of recognized typhoid carriers and their relation to gall-bladder troubles, some mention may be made of the positive Widal findings so often referred to in jaundiced patients before the carrier condition was recognized. According to Kohler (1902), who collected 614 references, which had appeared up to the spring of 1901, concerning the agglutinins in typhoid fever, the prevailing idea then was that the presence of bile elements in the blood-serum influenced the agglutinating power of the latter towards the typhoid bacillus. As a matter of fact, the bile itself, though it possesses in low dilutions an agglutinating effect on the typhoid bacillus, shows no greater agglutinating power over typhoid bacilli in persons dying of typhoid fever than in persons dying of other diseases.

By injecting into dogs and rabbits the various elements of the bile (taurocholic acid, etc.), or by creating artificial biliary stasis through ligature of the ductus choledochus, Kohler attempted to show that the agglutinating power of the serum towards the *B. typhosus* is artificially developed. For example, in one experiment before operation the serum gave no agglutination in a dilution of 1 in 10. After operation, when bile pigment was present in the urine, the serum gave a slight reaction at 1 in 60, and in another case a slight reaction at 1 in 20. It cannot be admitted, however, that the figures are at all significant, and further experiments by Venema (1906) showed that the addition of human bile to serum did not influence its agglutinating power towards *B. typhosus* or *B. paratyphosus*.

CARRIERS AND GALL-STONE DISEASE.

Quite a large number of carriers suffer from gall-stones, while in others, though symptoms may have been absent, a condition of cholelithiasis has been very frequently found, whether on examination post mortem or at operations directed towards bacteriological cure of the carrier condition. As early as 1892, Naunyn (1892) had observed that gall-stone troubles frequently occurred in persons who had suffered from typhoid fever.

Lentz (1905) was the first to direct attention to the association of gall-bladder complaint with the carrier state, but it was left for Forster (1908), of the Strassburg school, to develop this view more completely. The latter found that, out of a total of 194 convalescent carriers who continued to carry the bacilli for some weeks after convalescence, 29 per cent. were men, 45 per cent. were women, and 26 per cent. were children. On the other hand, out of 173 chronic carriers who continued to excrete the bacilli from one up to thirty years after the primary attack, 79 per cent. were women, 17 per cent. were men, and 4 per cent. were children. This striking preponderance of female chronic carriers over male (nearly 5 to 1) suggested a strong analogy to the relative gall-stone incidence in the female and male, which is approximately 3 to 1. As a matter of fact, 25 (*i.e.*, 14 per cent.) of the 173 chronic carriers referred to, presented gall-stone symptoms during life, while the remaining 86 per cent. had no such symptoms. This accords well with the known fact that 90 per cent. of all gall-stone cases present no symptoms during life. Similar percentages have been obtained by other observers—*e.g.*, G. Mayer (1910).

There has been considerable discussion as to whether the typhoid bacillus directly excites the formation of the gall-stone, and even forms a nucleus for it, or whether the stone is preformed, and is later penetrated by the typhoid bacillus. The question cannot yet be considered as settled, but the chief arguments on either side may with advantage be referred to here.

In the first place, the typhoid bacillus has been repeatedly isolated from the centre of gall-stones in cases of cholelithiasis operated on by the surgeon, and in chronic carriers either at operation or at autopsy (*vide* pp. 86-90). Individual instances of such findings need not be mentioned in detail, but I may refer here to a carrier case in which the typhoid bacillus has on two occasions been isolated from gall-stones passed in the fæces. This case was observed by the writer for two years. He is a medical man, and has kept accurate records of his gall-stone attacks, which he kindly placed at the writer's disposal. The primary typhoid infection occurred in November and December, 1896, and was a very severe one with two relapses. Convalescence was established at the end of February, 1897, and on August 24 of the same year he had his first attack of biliary colic, which was accompanied by slight jaundice and lasted four days. Two further attacks had their commencement on November 10 and December 13 respectively. In 1898 there was only one attack, commencing on January 14 and lasting five days. The patient enjoyed a respite from gall-stone colic till April, 1902, when five transient paroxysms, lasting each half an hour, occurred on April 5, 11, 14, 16, and 20. No stone was passed.

On April 21 a severe attack occurred, and on this occasion a mulberry-shaped calculus weighing 4 grains, and consisting of bile pigment, was found in the stools.

Transient colic attacks were experienced on May 4 and June 23, followed on July 17 by a severe attack lasting five days and accompanied by slight jaundice.

On July 27 there was a less severe attack lasting two days, and a calculus similar to the first was found.

In 1903 the first attack commenced on March 17, and lasted five days; a calculus was found. On April 11 a similar attack occurred, with passage of a calculus. There were also similar attacks lasting two days and with passage of calculus on May 12, June 2, June 11, July 3, August 18, and September 15.

1904: Attacks occurred on July 5, 7, and August 18, with passage of calculi. On October 1 there was a severe attack with renewal of colic on fifth day; two calculi were passed. On November 24 an attack occurred lasting three days; a calculus was passed.

Three years of freedom intervened.

1907: On November 23, 24, 28, and 30, December 27 and 30, there were transient attacks of colic unaccompanied by passage of stone.

1908: On January 2 occurred the severest attack yet experienced, requiring the administration of an anæsthetic; a stone was passed. On March 14 biliary colic began, and lasted three days. The stone passed on this occasion was submitted to bacteriological examination (at the Lister Institute), and found to contain typhoid bacilli. Since that date numerous examinations have been made of his fæces and of occasional gall-stones.

On March 24 he suffered from two days' illness; no stone was passed.

1909: On May 5, 6, and 7, transient attacks occurred, each lasting half an hour. Later on the 7th a severe attack ensued, lasting three days, and accompanied by passage of a stone. On October 3 prodromal colicky pains began at 11 a.m., and severe colic at 9 p.m., which entailed confinement in bed till October 6; a calculus was passed.

This last calculus, which was passed on October 6, 1909, was placed on cotton-wool in a pill-box, and was not handed over for bacteriological examination until November 3, 1909. It was a brown friable pigment stone of the size of a large pea. Owing to its rough, friable, and porous character, it was impossible to sterilize the exterior thoroughly. Accordingly, it was shaken in a tube of sterile broth, removed, dipped in alcohol, and flamed two or three times, and finally ground up in a mortar containing a small quantity of sterile broth. The washings and the stone emulsion were then immediately plated on bile-salt-lactose-agar. Next day the plates contained enormous numbers of typhoid bacilli in pure culture. The strain was agglutinated by an antiserum in dilution of 1 in 7,000, and was lethal for a guinea-pig of 250 grammes weight (intraperitoneal injection) in 0·5 c.c. of a forty-eight-hours broth culture. That the typhoid bacillus would be viable in a gall-stone after a month's sojourn in cotton-wool was not anticipated, and in view of the positive result two gall-stones, passed by the same patient on May 9, 1909, and December 29, 1907, respectively, were examined in a similar way on November 5, 1909. Neither, however, contained typhoid bacilli. Kramer (1907) had also observed that typhoid bacilli contained in apparently dried-up bile salts retained their vitality for a considerable time.

It is of interest to note that this carrier has enjoyed a complete respite from gall-stone colic during the past two years.

A case in many respects similar to the above was reported by Dean (1908). The carrier, who was also a medical practitioner, had passed through a severe attack of enteric fever twenty-nine years previously. Within three months of his illness he had an attack of acute pain in the gall-bladder region, and for more than a year thereafter he suffered from biliary crises at intervals of about three months. Jaundice was occasionally a feature of these attacks. Afterwards, however, the attacks became less frequent (one or two per annum), and they have never led to any interference with his medical work. His fæces showed on examination (in spring of 1908) enormous numbers of typhoid bacilli, but the urine was negative. His serum gave a negative Widal reaction. Since 1908 numerous examinations of his fæces have been made, with, as a rule, positive results. Neither of the above two cases is known to have caused infection in other persons.

Bacmeister (1907) reported the bacteriological examination of a series of twenty gall-stones from various cases. Of these, sixteen were sterile, and four contained bacilli in the centre—viz., *B. coli* (two cases) and *B. typhosus* (two cases). One of these latter was a female who died of typhoid fever in the fourth week of the disease. There was no evidence in this case of a previous attack of typhoid fever, and he considered it very unlikely that in three weeks the typhoid bacillus could cause the formation of a hard stone of the size of a cherry, although Mignot (1898), Droba (1899), Naunyn (1892), believed such rapid formation possible. Hertz and Adams (1910) calculated that, in their case reported above, the gall-stones must have taken less than sixty-eight days—probably not more than fifty days—to form. The evidence they assign, however, is not indisputable, as, although there was no history of an earlier typhoid infection, the authors explicitly state that the patient had occasionally suffered from a dull aching epigastric pain since the birth of her only child three years previously. In Bacmeister's view, stones found in recent cases of cholecystitis were as a rule sterile, while organisms were only to be found in old stones into which they had penetrated. The opposite view has been held by other observers—*e.g.*, Cushing—viz., that only recently-formed stones contain bacilli. Gilbert and Fournier (1896) had previously experimented with gall-stones and broth cultures of *B. coli*, and found that the bacilli wandered in when the stones were of cholesterin, but not in the case of other stones. Their experiments were repeated by Bacmeister, who placed gall-stones in both broth and bile cultures of *B. typhosus*. Most of the stones remained sterile, but in two cases (after eight days and twenty-four days respectively) the *B. typhosus* was recovered from the centre of the stone. One of these stones was a mulberry cholesterin stone of the size of a hazelnut, while the other was a faceted stone of the size of a cherry. They had been obtained from two women of thirty-eight and eighty-two years of age respectively. It may be noted that no mention is made of the history of these women or of the interval between the experiment and the obtaining of the stones. The possibility is not excluded that these cases had been carriers, and the typhoid bacilli may still have been viable in the stone, as in the case referred to above.

The fact that bacilli can penetrate into the interior of gall-stones is a point of great importance, but it by no means follows that in the genesis of gall-stones micro-organisms play an entirely passive rôle. The experiments of Gérard (1905), Kramer (1907), Bacmeister (1908), and others, go to show that embryonic gall-stone formation may be observed in test-tubes containing bile cultures of *B. typhosus*, *B. coli*, and other micro-organisms. The last-named observer found that *B. coli* and *B. typhosus*, *B. proteus*, and especially *B. pyocyaneus*, could cause a precipitation of cholesterin from filtered bile. True concretions were also found after prolonged growth on this medium. Their ability to produce such precipitates was much enhanced by employing unfiltered bile containing epithelial elements. Similar precipitates of cholesterin also occurred in sterile filtered bile in which no micro-organisms had grown, so that in the genesis of the pure cholesterin stone, at least, stasis alone can act as the exciting factor. The presence of epithelial elements or bacteria in the test-tube experiments merely accelerated and intensified this precipitation of cholesterin. For the genesis of the mixed cholesterin-chalk stone, however, they believed that a chronic inflammatory condition of the bladder wall was essential. Exner and Heyrovsky (1908) performed similar experiments with ox bile and human bile, and also with broth to which the bile salts had been added. They found that some micro-organisms, especially those of the typhoid group, could readily break down the bile salts (sodium glycocholate and sodium taurocholate), thus causing a precipitate of cholesterin.

In the light of these experimental results there would seem to be no doubt that the typhoid bacillus may play a part in the formation of gall-stones, but at present we are unable to say how far this formation is contributed to by other factors.

Our knowledge of the relationship of *B. typhosus* to the gall-bladder has been considerably enhanced by animal experimentation. So long ago as 1899, Blachstein (1899) and Welch (1899) in America demonstrated that in rabbits which had been inoculated intravenously by typhoid bacilli the gall-bladder might continue to harbour these organisms for a very long period, even up to 109 days.

Forster and Kayser (1905)—the former of whom, as I have already noted, elaborated the view that the gall-bladder was most probably the seat of vegetation of the typhoid bacillus in carriers—repeated the experiments of Blachstein and Welch with a view to reproducing the carrier state in the rabbit. They also found that after large doses given intravenously the bile might still be infective six weeks later. Typhoid bacilli could also be recovered in some cases from the upper intestine. Further, they made the important observation that in cases in which the bile was sterile the typhoid bacillus could occasionally be isolated from the gall-bladder mucosa. Similarly, in man at a very early stage in the disease the bacilli would reach the gall-bladder, and there set up definite lesions which might or might not be accompanied by distinctive clinical symptoms. According to Forster and Kayser, the bacilli would reach the liver by the blood, be excreted by the bile, and so reach the gall-bladder.

In the same year Doerr (1905) recorded the results of experiments undertaken to test whether the typhoid bacilli reached the gall-bladder by the downward route from the liver through the blood, or by the upward route from the intestine. They showed that bacilli appeared in the gall-bladder as early as eight hours after intravenous inoculation. When, however, the hepatic duct was ligatured the bile invariably remained sterile. Also when the cystic duct was ligatured no bacilli could be demonstrated in the bile, thus proving that the bacilli travelled by the bile, and not by the bloodvessels of the gall-bladder itself. These latter experimental results dealing with ligature of the cystic duct have recently been called in question by J. Koch (1909) and Chiarolanza (1909). The former (at the instigation of Frosch, who believed that not only the gall-bladder, but also the biliary tracts, and perhaps the liver itself, were seats of vegetation of the typhoid bacillus in carriers) investigated the histology of the gall-bladder mucosa in a fatal case of typhoid fever. The patient had died of heart failure in the third week of the disease.

The organ contained cloudy, slimy, green bile, and its walls were much thicker than normal. No stones were present. Typhoid bacilli were recovered from the gall-bladder wall, the larger biliary tracts, the mesenteric glands, renal pelvis, and small intestine, but not from the heart blood. On microscopical examination the mucosa of the gall-bladder was very much corrugated and papillated, and near the extremities of the papillæ typhoid nests were found with necrotic areas in their vicinity. The superficial epithelium had completely disappeared, and there was a marked inflammatory proliferation of the submucosal folds. A conspicuous feature was the close relationship of these typhoid nests to the minute end capillaries of the submucosal papillæ, suggesting that the bacilli had reached this situation solely by way of the bloodvessels. No organisms were demonstrable microscopically in the lumen. The experiments of Chiarolanza entirely supported this view. Even within two hours of intravenous injection, typhoid bacilli were recovered from the gall-bladder wall. Also, contrary to Doerr's results, bacilli were got from the gall-bladder when the cystic duct was ligatured. The histology of the rabbit's gall-bladder was essentially similar to that of the human case above referred to. The walls were thickened and infiltrated, and the submucosa very cellular, with papillary proliferations containing typhoid nests at their extremities. Sections of the bile tracts and the intestine showed parallel changes, and there was a marked small-cell proliferation in the portal areas of the liver itself. It would appear, therefore, that the main, if not the only route, of the typhoid bacilli to the gall-bladder is by the vessels of that organ itself. In any case this is the chief route to be considered in drawing deductions as to the possible value of surgical interference with the gall-bladder as a remedy for the carrier state. The bacilli vegetate in these submucosal nests, and not in the bile itself. The latter passively receives accessions of typhoid bacilli from ruptured nests either in the bladder mucosa or in the biliary tracts.

Morgan (1911) has recently reported on the examination of a series of twelve rabbits which had been inoculated intravenously with *B. typhosus*. One of his objects was to determine whether a carrier condition in a rabbit could be diagnosed by examination of the fæces. In two instances only was the *B. typhosus* recovered from the fæces, one eight days after inoculation, and the other eleven days. The method, therefore, was not satisfactory, as in one case at least the *B. typhosus* was recovered at death from the bile and gall-bladder wall two and a half months after inoculation. The mucosa of the gall-bladder in this case showed several inflammatory foci near the tips of the shaggy papillæ.

I shall conclude this section with certain general considerations which have been put forward in explanation of the carrier state. In the first place, with regard to the preponderance of cholelithiasis in the female, various reasons have been assigned, such as the wearing of tight corsets, frequent pregnancies, etc., causing portal stasis.

Similar factors may, however, according to Forster, play a part in rendering males liable to carry the bacillus indefinitely after the primary attack. Thus, Forster (1908) mentions the case of a man who contracted typhoid fever two years after an operation for appendicitis. After his recovery his wife took typhoid fever, and the husband was then found to be a carrier.

Owing to the appendix operation and ensuing inflammation, anatomical changes had taken place in the peritoneum, thus altering the circulatory conditions and probably predisposing to the carrier state. This explanation by Forster may have some foundation in fact, but further data must be awaited before one can draw any definite conclusions on this point. One may note, however, that Lentz (1905) had already suggested that the greater liability of women to become carriers probably bore some relation to the circulatory disturbances incidental to pregnancies and to overexertion in household duties.

An interesting view put forward by Prigge (1909) in order to explain the higher proportion of women carriers may also be noted here. Whereas, according to Prigge, the incidence of enteric fever on females reaches a maximum between the ages of fifteen and twenty years, the probability that a woman will become a chronic carrier increases gradually from the fifteenth to the forty-fifth year. This fact suggested to him the possibility that predisposition to the carrier state might be induced by the menstrual and puerperal blood-losses. There is some evidence that these physiological crises are accompanied by a diminution of the alexin content of the blood-serum, which would render the subject for the time being more vulnerable to an infecting micro-organism. In support of this view, it is alleged that enteric fever (often mistakenly diagnosed as puerperal fever) is of frequent occurrence at child-bed. If to the general blood-changes at these seasons there be added the pressure caused by a gravid uterus on the biliary system, there would, it is maintained, be a sufficiency of factors predisposing to the carrier state. As Bacmeister showed in his test-tube experiments, stasis fluids accelerate the precipitation of cholesterin by bacteria. If, therefore, a woman who has previously had an attack of cholecystitis contracts enteric fever, the chances of her remaining a carrier after her attack would be intensified.

Fornet (1909) has formulated the view that the carrier state is to be regarded as a consequence of established immunity to the typhoid bacillus, and that, in fact, the bacilli discharged by the carrier may not necessarily be descended from those which caused the primary infection. A reinfection takes place which, according to Fornet, is not accompanied by any clinical symptoms. The region attacked by the bacilli in this reinvasion would have acquired, in consequenec of the primary attack, such a tolerance to the micro-organism as to render its saprophytic existence possible.

This view was based by Fornet on the following considerations :

Klinger had found for the year 1907 of the typhoid campaign a carrier output of only 0·9 per cent., whereas most individual observers have obtained a much higher percentage (see earlier sections). Fornet thinks, therefore, that persons may not become carriers as the result of the primary infection, but only after a second symptomless infection. The carrier statistics for the year 1908 (compiled by Fornet) are adduced in support of his view. Thus, in that year ninety-one carriers (temporary and chronic) were discovered in the course of the typhoid investigations, and, as Klinger had already noted in his series (p. 24), the group of chronic carriers was almost exclusively made up of adults, whereas among the temporary carriers children formed a large contingent (30 per cent.). Fornet argues that, as the adult has probably had more opportunities of having passed through an attack of typhoid fever than the child, the prospect of his becoming a carrier as the result of a second infection would be correspondingly greater. Accordingly, if his view that the carrier state is the culmination of a symptomless reinfection be a correct one, he would expect to find among the chronic carriers of the year 1908 a greater proportion of adults who had already had typhoid than of adults who had not so far suffered from the disease. As a matter of fact, 59 per cent. of the chronic carriers had already had typhoid, while 41 per cent. had not yet had the infection. Among the temporary carriers, on the other hand, 74 per cent. had not yet had the disease, while 26 per cent. had recovered from a primary attack.

It does not appear to us valid to employ these statistics in this way, in view of the difficulty of determining whether a person who happens to be a temporary carrier has really passed through a typhoid infection or not. While recognizing the important distinctions that separate the two groups of chronic and temporary carriers, particularly in the matter of age and sex, it would be unjustifiable in the present state of our knowledge to lay stress on the numerical distinctions between the carriers in each group who have had a previous infection and those who have not. Indeed, from Klinger's collected statistics up to 1907 (see p. 24) it is seen that 80 per cent. of the carriers had had a primary infection, while 20 per cent. had not. Of the temporary carriers, 43·6 per cent. had had a primary infection, while 56·4 per cent. had not. Thus the relative percentages in this latter group differ considerably from those of Fornet for the year 1908.

Finally, in view of the gradual accumulation of cases which have been traced bacteriologically from the convalescent stage onwards to the chronic carrier state, such a theory as that of Fornet would seem at present uncalled for. It is undoubtedly, however, an interesting speculation, and it remains to be seen what amount of support is lent to it by the results of experimentation on the saprophytic growth of pathogenic bacteria in the immune organism.

Dr. Theodore Thomson (1910) would suggest that a view such as that of Fornet might afford an explanation of the fact that in towns like Lincoln and Maidstone, which suffered severely from water-borne typhoid infection, there has been subsequently no undue incidence of typhoid fever. Such towns would contain, not actual, but only potential chronic carriers—*i.e.*, persons who had recovered from one infection, and who in response to a symptomless reinfection would become actual carriers.

In the absence of valid evidence in support of Fornet's hypothesis, the writer is unable to subscribe to this suggested explanation of the facts. If one assume that the facts with regard to these towns are as stated, and that all other explanatory factors—such, for example, as the occupation of the recovered cases, their social status and personal hygienic habits, their participation in emigration, etc.—may be excluded from consideration, there still remains the possibility that the facts may be due to a real absence or paucity of carriers. In a water-borne epidemic in which, let us suppose, the majority of the attacked have consumed the contaminated water, the particular strain of *B. typhosus* gets little opportunity of becoming accommodated to the human organism, whereas an endemic strain that has had many opportunities of passage, or a carrier-strain that has sojourned for long periods in a human carrier, may conceivably be more highly endowed with those properties which permit of its continued vegetation in the body after the infection is past. In short, the carrier output may be a function of the serum fastness of the strain, and in an explosive water-borne epidemic the yield of carriers may be small. The hypothesis is at least capable of proof.

PHYSICAL DISABILITIES OF THE CARRIER STATE; AUTO-INFECTION, ETC.

The question is frequently asked whether the typhoid carrier suffers in bodily health as the result of the carrier state, or whether *ceteris paribus* he or she remains a normal healthy individual. In general it may be said that the carrier who has no definite gall-bladder or genito-urinary symptoms is little if at all inconvenienced in bodily health by the fact that the typhoid bacillus has acquired a permanent habitat in some portion or portions of his anatomy. Occasionally headaches are complained of, particularly by urinary carriers, and measures taken to arrest the typhuria have reacted favourably on the general well-being of these cases.

G. Mayer (1910), however, has laid stress on the fact that certain carriers of the intermittent type have been observed to suffer from periodic intestinal disturbances after the primary infection. He states that these are specially likely to occur at certain seasons—*e.g.*, in midsummer, when winter merges into spring, autumn into winter—and that at such seasons it is advisable to exercise strict bacteriological supervision over declared carriers. Also it must be admitted that, in persons of nervous temperament who are aware of their condition, there is good evidence that the knowledge of their having caused disease in other persons, the consequent anxiety and the necessarily harassing precautions to be taken with regard to disinfection, etc., develop a form of neurosis which may react injuriously on the general bodily health. Such cases have not infrequently been met with, and the fact that the carrying-state may have this unfortunate and serious issue calls for the greatest tact on the part of those whose duty it is to exercise supervision over carriers.

In this section it is proposed to discuss mainly those cases in which a recognized carrier suddenly develops a train of symptoms pointing to a general infection by the bacillus he or she is carrying. Only a few examples have so far been reported in which an auto-infection has been indicated, but they are of such importance for an understanding of the carrier state that they will be referred to in some detail.

The first of such cases was recorded by Levy and Kayser in 1907. The patient (female, aged thirty-five years) was an inmate of the Hordt Asylum, an institution in which thirteen other carriers were discovered at various times (1904 and 1905). She was admitted to the asylum as an epileptic on March 25, 1903. During April and May of the same year she suffered from a remittent fever, which was diagnosed as typhoid fever, although no Widal or other bacteriological test was made. Two years later, when carriers were being sought for to explain the typhoid epidemics in the asylum, this woman was found to be a carrier (October 16, 1905). Further examinations of her stools on November 24, 1905; January 25, February 6, March 2, April 9, April 27, May 28, June 11, and June 29, 1906; were positive, while the urine remained negative. On October 17, 1905, she had been isolated along with the other carriers, and a year later (October 8, 1906) she became ill with pain in the stomach region and constipation. On October 12 she was put to bed, and death took place on the 18th, following a febrile attack associated with severe pulmonary symptoms. The autopsy (October 19) revealed hypostatic pneumonia of the right lower lobe and a slightly enlarged spleen. The brain appeared normal. The gall-bladder contained a cholesterin stone of the size of a bean. Its peripheral layers were sterile, but from the centre the *B. typhosus* was recovered. This bacillus was also isolated from the liver blood, the spleen, the bile, and gall-bladder wall. Though the post-mortem examination was performed nineteen hours after death, the bacteriological results, particularly the finding of typhoid bacilli in the spleen and liver blood, and the absence of other micro-organisms, led to the conclusion that the carrier had succumbed to a general infection by her own bacillus. The ill-defined pains in the stomach region on October 8, 1906, might very well fit in with gall-bladder trouble, as it is well known (Naunyn, 1892, Riedel, 1905) that pain arising from disturbance of the latter organ may be referred to the stomach region. The discovery of the bacillus in the centre of the stone was naturally held by Levy and Kayser to give strong support to Forster's view that the gall-bladder is the seat of vegetation of the typhoid bacillus in carriers.

The second case reported by Grimme (1907) as one of auto-infection will be referred to here, though the actual bacteriological proof that the woman had been a chronic carrier was wanting. The patient (aged fifty-two years) was also an inmate of an asylum. Suddenly, when at work, she developed epileptiform convulsions and became unconscious. Her temperature was 38° C., and there was slight splenic enlargement. Vomiting occurred while the patient was being examined. On the second day jaundice developed, and the liver and spleen increased in size. There was no rash. On the third day a Widal test was positive (1 in 800), and the *B. typhosus* was got from the blood and fæces. Death occurred on the twelfth day. At the autopsy a cancer of the gall-bladder was found, which had led to the closure of the ducts, and so to jaundice. One gall-stone was present, but the typhoid bacillus was not recovered from it. The spleen, bile, and peritoneal exudate, however, contained typhoid bacilli. Peyer's patches were not swollen, but appeared atrophic, with bluish pigmented patches in them like the remains of some previous pathological condition. That the patient had had typhoid fever previously was rendered probable from the fact that in 1904, when outside the institution, she had suffered from a febrile attack with diarrhœa, slight splenomegaly, and a doubtful rash.

A very similar case, affecting also a female lunatic (sixty-four years of age), is reported by Kamm (1909). This woman in November, 1901, passed through a typical attack of enteric fever. On March 12, 1906, in the course of a systematic examination of the female inmates, she was discovered to be a carrier. Positive results were obtained from her stools on March 8 and 20, April 9 and 27, May 25, June 2, 12, and 20, July 28, August 8 and 14, October 19, and December 9, 1906, but the urine was invariably free from typhoid bacilli. In spite of all therapeutic efforts to free the patient of her typhoid bacilli, seventy-two out of the eighty-five examinations of her stools during 1907 were positive. In February and March, 1908, pulmonary troubles pointing to phthisis intervened, and tubercle bacilli were found in the sputum. Death occurred on March 16, 1908, after an attack of cerebral apoplexy lasting four days. The autopsy revealed carcinoma of the gall-bladder encroaching on the liver, cholelithiasis, secondary growths in liver, pleuræ, lungs, and retroperitoneal glands. The ductus choledochus and ductus hepaticus were normal. The cystic duct was thickened, and its lumen so narrowed that a sound could not be passed through the opening into the choledochus. The gall-bladder was much dilated, and contained 195 polyhedral stones, of which the largest weighed 18 grammes. The spleen was enlarged, but not the mesenteric glands. From the gall-bladder, the biliary tracts, the interior of the large stone, the right and left lobes of the liver, the lungs, bone marrow, and spleen, and all portions of the intestinal tract, the typhoid bacillus was recovered. It was not present, however, in the heart blood, the small stones, or the cervical, mesenteric, and retroperitoneal glands. How far this general infection by the typhoid bacillus had contributed to the patient's death it was impossible to say. The author refused to consider that the typhoid bacillus had merely invaded a weakened organism, for the reason that, in another case observed by him, where the bodily enfeeblement was equally great, there was no general distribution of the typhoid bacilli.

The instances I have mentioned so far have all been fatal cases in which the auto-infection was verified by extensive bacteriological examinations made after death. The literature of this subject also contains not a few examples of typhoid relapses in typhoid carriers which did not lead to a fatal issue.

Mayer (1910), in the course of his typhoid investigations in the Bavarian Pfalz, gives a series of such cases which are of considerable interest, inasmuch as the carriers affected were generally intermittent carriers. After the primary attack of typhoid fever the bacilli could be demonstrated only at intervals in the fæces. With the onset of the relapse the excretion of typhoid bacilli became again a prominent feature. There was evidence, too, that the Widal reaction, which may have been negative after the primary attack (though the person was still excreting the bacilli intermittently), became positive during the relapse, to disappear again after recovery.

An interesting case of acute abdominal infection in a typhoid carrier has also been reported by Gardner (1910). The patient (male, aged fifty-six years) had an attack of typhoid fever in 1906, when he was in bed for ten weeks. In 1900 he had suffered from peripheral neuritis which was attributed to the presence of arsenic or lead in the beer "of which he drank a good deal at that time." The illness reported by Dr. Gardner commenced on January 26, 1910, with pain in the abdomen and nausea, and lasted about a fortnight, the symptoms throughout being those of an acute cholecystitis. There was only very slight icterus, but the fæces after a calomel purge were "semi-solid, homogeneous, slaty grey, and very offensive." No bacteriological examination of the stools was made until the occurrence of two cases of typhoid fever in the patient's household shortly after his recovery suggested the possibility that this man might be a typhoid carrier. This proved to be the case. His serum gave a positive Widal reaction, and his fæces were examined by me on April 4, 1910, with positive results.

Further examinations: April 21, 1910, positive; May 7, 1910, negative; May 19, 1910, negative. The urine was always negative. An examination of this man's fæces was made by the writer in April, 1912, and *B. typhosus* was found. No further cases had been traced to him in the interval.

Arnsperger (1910) has recorded the occurrence of typical typhoid fever in a female who sixteen days previously had an operation for gall-stones (cholecystectomy with drainage of ductus hepaticus). The probability was that the woman had been a typhoid carrier, and that owing to the surgical interference an auto-infection had developed. No similar cases are recorded in the literature, but it is not improbable that some of the puzzling febrile conditions occurring after gall-stone operations may be due to this cause.

Mention must also be made of the possibility of infection of the fœtus in pregnant carriers, either as the result of a blood-invasion by the bacillus consequent on the disturbances during pregnancy and child-bed, or more probably in consequence of an actual cholecystitis during child-bed, as in a case reported by Mayer (1910), where the child was born with typhoid fever. In a later section reference will be made to the successful isolation of the typhoid bacillus from the blood of the umbilical cord, at the confinement of a carrier who has been under bacteriological observation for a considerable time. The child, so far as I am aware, was quite healthy at birth.

TREATMENT OF TYPHOID CARRIERS.

Intestinal Cases.

Forster (1908) has stated that if we can cure carriers we can get rid of typhoid fever, and, indeed, it may be that only time and further experience are necessary to establish the truth of this dictum. Unfortunately, it must be admitted that hitherto no certain method has been devised of rendering carriers typhoid-free. That cases have occurred in which the excretion of typhoid bacilli has ceased spontaneously is undoubtedly true, the cessation perhaps coinciding with a healing of the gall-bladder trouble. It has even been noticed, as in a case reported by Forster (1908), that the excretion stopped after an acute attack of gall-stone colic, which was the first that this female carrier had experienced. We cannot exercise too much caution in accepting these spontaneous cures, as it has been repeatedly demonstrated that an intermittent period may extend over many months, and, further, it must be remembered that our bacteriological methods are not yet sufficiently delicate to detect minimal quantities of typhoid bacilli in excreta. As an illustration of the necessity for caution in interpreting these so-called "cures" in temporary carriers, a personal experience may be quoted. Mrs. C. had enteric fever in July and August, 1908, and her temperature had fallen to normal on the 24th of the latter month. In late convalescence she suffered from gall-stone complaint. On October 30 her fæces were examined, and found to contain typhoid bacilli. A positive result was also obtained on December 8, 1908, but further examinations in January, March, April, May, July, and August, 1909, were negative, and accordingly this case was considered to have belonged to the category of temporary carriers. In January, 1910, however, another examination of her stools revealed enormous numbers of typhoid bacilli, so that the woman is to be regarded in future as a chronic carrier.

With a view to determining whether spontaneous cures occurred, Prigge (1910) made monthly examinations, in the course of the previous three years, of his chronic and transitory carriers, with the result that, of twenty-eight chronic female carriers who had excreted typhoid bacilli over a year, one only could be struck off the list. However, in a footnote to his paper he mentions that this woman was again excreting typhoid bacilli in October, 1909, after three years' intermittence.

In other cases he noted intermittent periods extending from one to two and a half years.

Chemotherapy.

The drug treatment of intestinal carriers has been entirely ineffective in ridding these persons of their typhoid bacilli. Salol, beta-naphthol, sodium salicylate, calomel, bile and its salts, turpentine-oil, sodium bicarbonate in large doses, choloform, etc., have been employed, with no effect or only a temporary one on the excretion of the bacilli.

So far as the results of drug treatment are concerned, all that one can conclude at present is that internal antiseptics may, if pushed to their physiological limits, offer some slight prospect of success. Our knowledge of the pathology of the carrier state makes it difficult to conceive that any treatment other than an intensive one should exercise the slightest effect on indolent typhoidal lesions in the gall-bladder and bile tracts.

The fact that it is possible to reproduce the carrier condition in rabbits by a single intravenous inoculation of the typhoid bacillus has opened up a new field for chemotherapeutic research, which it is hoped may have some practical application to the treatment of the human carrier. The success so far achieved in rendering the rabbit carrier typhoid-free cannot be considered in any way striking, but the method is at least promising; and in view of the recent successes with chemotherapy, not only in lues, but also, perhaps, in certain bacterial infections — *e.g.*, experimental anthrax infection (Becker, 1911; Bettmann and Laubenheimer, 1912), pneumococcic infection (Morgenroth, 1911)—its further development is abundantly called for. Conradi (1910) employed chloroform in an emulsion of milk and cream, which he passed by means of a sound into the large intestine of the inoculated rabbit. The mixture was given daily for five days as a rule, and the rabbits were killed not later than the first fortnight after inoculation. Of a series of twenty-one rabbits so treated, sixteen were found to be typhoid-free, while all the controls (twelve) remained infected. Another series of rabbits was similarly treated, and killed at a much later period after inoculation. To determine whether these rabbits were still carrying before the commencement of treatment, puncture of the gall-bladder was performed after laparotomy, and the bile bacteriologically examined. The result was that five chronic rabbit carriers became typhoid-free, while three untreated chronic carriers remained positive. Conradi's method has not yielded such striking results at the hands of other workers. Thus, Hailer and Rimpau (1911), using Conradi's technique, found that 7 out of 10 rabbits treated intrarectally became typhoid-free—*i.e.*, 70 per cent.—while 5 out of 18 controls were also typhoid-free at the same period after inoculation (30 per cent.). A large series was also undertaken by Bully (1911), using the same technique. Excluding all the animals which died from the toxic effects of the chloroform itself, there remained 30 treated rabbits, all of which proved at the end of the experiment to be typhoid-free. Of the 30 untreated controls, however, 60 per cent. were also typhoid-free at the same period. It would appear therefore, as Morgan (1911) has pointed out, that spontaneous cure has to be reckoned with in these carrier rabbits, and that, therefore, very much larger series of animals than those hitherto employed must be experimented with if a correct estimate of the therapeutic influence of chloroform is desired. Both Conradi and Bully have tested the therapeutic effect of chloroform in two human typhoid carriers (females)—(Gelodurat capsules per os, 0·5 gramme $CHCl_3$ + 0·5 gramme olive-oil), but no obvious cessation in the excretion of typhoid bacilli resulted from the treatment.

Sour Milk Therapy.

The administration of milk soured with lactic acid bacilli has been vaunted by some observers as affording an apparently permanent cure. Thus, Liefmann (1909) gave Yoghurt, in quantities of $\frac{1}{3}$ to $\frac{2}{3}$ litre daily, to two female asylum carriers, and observed that one week after the commencement of the treatment the stools in both cases were negative. After seven weeks the stools of one of the cases were again positive, but later examinations were negative. The last examination (there were only eight in all in each case) was made at the end of the eleventh week. Evidence derived from such a short period of observation proves nothing, not even that the temporary cessation was attributable to the treatment employed.

Three asylum carriers (Thomson and Ledingham, 1910), who have been under bacteriological supervision since the latter part of 1907, received sour milk (½ pint three times a day) daily during the period February to December, 1909, without any appreciable effect on the excretion of typhoid bacilli in the fæces during the administration of the milk.

Captain Fawcus, of the Army Medical Department (1909-1910), has reported fully on the treatment of army carriers by lactic acid bacilli. Two carriers received a course of Bulgarian bacilli grown in diluted malt extract, commencing with a dose of 25 c.c. of the culture. No improvement whatever took place in one case except a temporary diminution in the numbers of bacilli excreted, after administration of the doses. The second case, however, reacted more favourably to the treatment. The course was commenced on March 8 with a dose of 25 c.c., and was continued till May 28, when 250 c.c. were being given daily. On April 29 the fæces were apparently typhoid-free, and from that date they remained so. The man was discharged to duty on July 23, having been free from typhoid bacilli for three months. Further data with regard to this case will be awaited with interest.

At Netley, Major Cummins (1910) had no success with this method of treating intestinal carriers.

Zweig (1910) has employed Lactobacillin in two carriers, and is inclined to support Liefmann in his advocacy of this mode of treatment. In Zweig's cases the bacilli disappeared after the commencement of the treatment, and were not demonstrable during the succeeding three months. Only six examinations, however, were made during that period.

Surgical Treatment.

We now come to consider those attempts which have been made to abolish the carrier state by surgical interference with the gall-bladder. Naturally, when the view was put forward that the gall-bladder is the main seat of vegetation of the typhoid bacillus in intestinal carriers, operative interference directed towards improvement of the gall-bladder condition suggested itself as a possible remedy for the carrier state. The findings at such operations and at post-mortem examinations, which in some instances subsequently took place, are of much interest. I therefore propose to refer in some detail to all those cases which have been treated surgically.

Dehler (1907) operated on two female asylum carriers who had given rise to four cases of typhoid fever, including one fatal case.

CASE 1 (aged forty-six years) presented no history of having passed through an attack of enteric fever. Her fæces were regularly examined every three weeks, and in thirty-seven out of the thirty-nine examinations made, typhoid bacilli were present. They were not found in the urine or blood. Her blood-serum gave an agglutination reaction of 1 in 50, and often 1 in 100. There were no symptoms pointing to gall-bladder trouble.

On August 20, 1906, an operation was performed. The gall-bladder was released from surrounding adhesions and opened. Two cherry-sized stones were removed, one of which had dilated the cystic duct. Typhoid bacilli were present in the bile, but not in the stones. Drainage was then carried out through a tube led into the dilated cystic duct. The bile regularly contained typhoid bacilli up to the twenty-first day. It then remained negative until October 11, 1906, when it was again positive. After the cystic duct could no longer be opened owing to cicatrical formation in the depth, the secretion from the fistula ceased to contain *B. typhosus*. The fistula cicatrized completely about the middle of December.

Three days before the operation typhoid bacilli were found in the fæces. Subsequent to the operation twenty-six samples of fæces were examined in the period August 24 to October 17, and fifty samples between October 17 and February 19, 1907, and all were negative. The urine remained typhoid-free, and the agglutinins also remained at the same titre as before the operation. Dehler noted that so long as the bile flowed freely and speedily from the fistula the *B. typhosus* was scarce, and was, indeed, for four weeks not demonstrable in the bile, but that as the fistula narrowed, and the bile flowed more slowly, the typhoid bacilli got time to propagate in the bile, and were therefore very numerous.

Later still, as the fistula closed and the gall-bladder cicatrized, the bacilli disappeared, as there was no further opportunity of vegetating in stagnant bile. The fact that the fæces remained negative suggested that any bacilli carried down directly from the bile paths into the intestine were overgrown by other bacteria.

Also it was considered not improbable that the discharge of the bacilli from individual portions of the liver and their bile tracts would gradually cease completely. To hasten this action, cholagogues, such as calomel, etc., were given for two months.

In a later communication (October 22, 1907), Dehler (1907) notes, with reference to the above case, that, on three occasions out of 176, typhoid bacilli were got in small numbers in the fæces, but believed that these few positive results might be explained by accidental mixing up of samples from other carriers. Up to February, 1907, the agglutination titre remained at 1 in 100, in March and April it fell to 1 in 50, and during May, June, and July, it was quite negative. The patient remained in excellent health, and the symptoms of intestinal catarrh, from which she had previously suffered, disappeared.

Case 2 (aged forty-five years) had no record of typhoid fever, though she had an illness nineteen years previously which might possibly have been an anomalous attack of this disease. In July, 1904, her serum had given a positive Widal reaction, but it was not till January 3, 1905, that typhoid bacilli were demonstrated in her fæces. During 1905, 9 samples of fæces out of 16 were positive, and during 1906, 5 out of 10. The urine was always negative. From January to April 9, 1907, 16 samples were positive out of 20, and 2 urine samples were positive out of 14. No gall-bladder symptoms were present during the last three years. Internal remedies had been tried, with no result. On April 10, 1907, the gall-bladder was opened and found to contain several small stones which were sterile. The bile was clear, and contained numerous *B. coli* and moderately numerous typhoid bacilli. Drainage was carried out as in the last case.

The bile that drained away during the first few days after operation contained typhoid bacilli, and these disappeared as the bile flow diminished. After the ninth day from the date of the operation they were found only on two occasions in the fæces—viz., May 25 and July 3, 1907 (out of 30 samples). Of these 30 samples of fæces, 28 were negative; the blood and urine remained always negative. The aggutination titre on July 31, 1907, was positive in 1 in 100, but on August 16, 1907, a negative reaction was obtained.

In the foregoing instances the surgical interference was confined to drainage of the gall-bladder; in those that follow, removal of the gall-bladder was resorted to.

Grimme (1908) reported that he had had the operation of cholecystectomy performed in a female asylum carrier in a Göttingen asylum. She had never shown symptoms pointing to implication of the gall-bladder.

At the operation (performed by Braun) numerous small stones of the size of peas (thirty to forty) were found in the gall-bladder. No inflammatory changes were present, but the bile and also the interior of the stones contained typhoid bacilli. The gall-bladder wall did not contain them. Fifteen days after operation the *B. typhosus* was found in the fæces, but not at a later period. The period of observation, however, was only fifty-five days, as the patient had to be discharged from the asylum. In a later paper by Fromme (1910), however, there is a note to the effect that the excreta of Grimme's patient were examined on August 18 and 22, 1910, with negative results.

Loele (1909) reports the next case, also a female lunatic, aged fifty-one years. This woman had typhoid fever during October and November, 1908, but during convalescence no typhoid bacilli were demonstrated in the fæces.

At Christmas, 1908, she had an attack of gall-stone colic with jaundice, and the fæces were now positive. There was a palpable tumour in the gall-bladder region. Her serum gave a reaction of 1 to 2,000, but the blood and urine were sterile. An operation was carried out on February 16, 1909. The gall-bladder was very adherent and difficult to remove. Between it and the stomach was an abscess containing a stone. During the operation the duodenum was perforated. The cystic duct was quite stenosed. The hepatic duct was drained, and the laparotomy wound closed except for the drainage-tube and plug.

On February 17 a large flow of bile occurred, and on following days the contents of stomach and duodenum appeared with the bile. Death took place on February 20. The gall-bladder contained pus and twenty-one stones of the size of hazelnuts. The bacteriological results in this case are of great interest.

The gall-bladder pus contained typhoid bacilli, as also did the gall-bladder wall. On the first day ofter operation the bile contained numerous typhoid bacilli. On the third day the fæces also contained a few typhoid bacilli. The gall-stones were found to be sterile internally.

At the autopsy cicatrices of typhoid ulcers were found in the small and large intestine, and bacteriological examination revealed typhoid bacilli in the following situations : Small intestine (upper, middle, and lower portions), transverse colon, liver, spleen, and heart blood. The urine was negative.

Loele concludes that the typhoid bacilli in the fæces did not come from the gall-bladder, for the following reasons : The gall-bladder was quite closed off by stenosis of the cystic duct, and contained pus, but no bile. The bacilli may have grown in the dilated choledochus or in the intestine itself, either after wandering in from the bile tracts or after getting accustomed to the small intestine. The smallest bile tracts in the liver were negative.

He does not think that removal of the gall-bladder in this case would have done the slightest good.

It is interesting to note that he found no typhoid nests microscopically in the bladder wall. He thinks the stones were certainly present before the typhoid attack, though they gave rise to no symptoms. The fresh attack had caused new inflammatory changes and empyema. His conclusion, therefore, was that cholecystectomy can be of no use if the seat of vegetation is in the bile tracts or in diverticula of the upper intestine, and that in no circumstances is the operation justifiable in carriers without positive palpatory evidence before operation.

We have seen that in all the carrier cases mentioned above, which have been operated upon or have come to autopsy, cholelithiasis has been invariably present. The following case, reported by Kamm (1909), which succumbed to pneumonia before the contemplated operative procedures could be undertaken, is of interest as showing that gall-stone formation may be absent in chronic carriers. The patient was a female lunatic (sixty-one years old) who passed through an attack of enteric fever in March, 1906. Typhoid bacilli were present in her stools during the attack, and were also demonstrated on the following dates : April 9, May 7, May 28, June 2, June 11, July 28, September 11, and November 7, 1906. Isolation had an unfavourable effect on this woman, who suffered from chronic mania. In 1907 typhoid bacilli were found in the fæces (but not in the urine) on the following occasions—viz., January 18, March 15, June 10, and July 26. The female warder who attended to this patient contracted enteric fever on October 18, 1907. The operation for removal of the gall-bladder was arranged for October 30, but had to be deferred owing to the onset of croupous pneumonia. Death took place on November 20, 1907. At the autopsy, in addition to the pulmonary lesion (croupous pneumonia of right lower lobe), there was marked interacinar cirrhosis of the liver, but the gall-bladder showed no inflammatory changes and contained no stones.

Typhoid bacilli were recovered from various parts of the liver, the gall-bladder, and the duodenum, but not from any other organ. The gall-bladder on microscopic examination showed complete loss of surface epithelium, and in the innermost layers of the mucosa numerous large masses of micro-organisms were found, some of which resembled the typhoid bacillus morphologically, and did not retain Gram's stain. It should be mentioned that the post-mortem examination was carried out twenty-eight hours after death, and that organisms of the *B. coli* type were invariably associated with the *B. typhosus*. There was no evidence whatever that the typhoid carrier state had contributed to the fatal issue of the croupous pneumonia.

It is unfortunate that Kamm does not mention specifically whether the pneumonic areas in the lung were bacteriologically examined.

Three adult females, not known to be carriers, were operated on by Fromme (1910) for gall-stone disease. In all cases cholecystectomy was performed. The operation in the first case took place on August 23, 1909, when the bile was found to contain *B. typhosus*. Examinations of the stools were made on August 3, 6, and 10, 1910, with negative results. In the second case operation was performed on March 4, 1910. On March 17 and 24 the fæces contained typhoid bacilli, but the results on August 1 and 5, September 7 and 9, were negative. The third case ended fatally.

From such data it is quite impossible to judge whether the typhoid depots in the biliary area were completely exterminated.

I conclude this review of the operative treatment of carriers with the reflexion that no trustworthy evidence of permanent cure has so far been forthcoming. As I have indicated in a previous section, it may well happen that, in cases of cholecystitis occurring at an early period in typhoid convalescence, surgical interference may be followed by a complete disappearance of typhoid bacilli from the fæces; but in long-established cases, where the infective germs have acquired a permanent footing, not only in the gall-bladder, but also in the biliary tracts and duodenal recesses, the prospects of success by operation directed solely to the gall-bladder are extremely small. No definite verdict, however, on the efficiency or otherwise of this method can be pronounced until the cases so treated have been under bacteriological supervision for at least one or two years thereafter. In a recent paper, Dehler (1912) brings forward further evidence in support of his view that radical operative measures afford a good prospect of complete cure.

Vaccine Therapy.

The treatment of intestinal carriers by typhoid vaccines has, it must be confessed, been unsuccessful or indecisive, though much was hoped from this method. As long ago as 1902, Koch suggested the employment of typhoid vaccines as a remedy for the carrier state. Thomson and Ledingham (*loc. cit.*) have treated five female carriers in this way with entirely negative results, whether stock vaccines or homologous vaccines were employed. In most of the cases where serological examinations have been made, we have noted a marked rise in the agglutinins, but in a recent case treated solely with the homologous vaccine no appreciable alteration took place in the agglutination titre. In a recent report by the Director-General of the Army Medical Service (1909), an account is given of the vaccine treatment of an intestinal carrier, Private L., both with stock and homologous vaccines, and a temporary cessation in the excretion of the germs in the stools was noted during the course lasting from February to May, 1909. Later, this case received X-ray treatment in the region of the gall-bladder. The carrier presented symptoms of slight cholecystitis, and this form of treatment might, it was hoped, bring about an increase of phagocytosis in the walls of an inflamed gall-bladder.

On August 6, 1909, the treatment was begun, the gall-bladder region being exposed for three minutes to a 3-ampère current in a tube with a 6½-inch spark-gap : (report by Cummins, 1910). Exposures were given three times a week for three weeks, and during this time and for three weeks afterwards the stools were typhoid-free. Positive results were, however, got on September 20, 23, and continuously from October 4 to October 21. Another X-ray course was commenced on October 20, and ended on November 15. On November 1 the stools were positive, but examinations on November 5, 9, and 12, and December 6, were negative.

The patient left hospital on November 16. The outcome of this treatment, as perhaps showing some inhibitory action on the discharge of bacilli, is certainly interesting and suggestive, but at present it would be premature to signalize this method as affording a prospect of permanent cure. As a matter of fact, the discharge of bacilli by the patient had been intermittent before commencement of the treatment. The method, however, deserves a further trial. The fæces and urine of this man, who is now a civilian, were examined by the writer on March 3, 1910, with negative results, but on June 4, 1910, the *B. typhosus* was isolated from his fæces, so that he cannot be considered as cured.

In another army carrier the method was tried, but without the slightest effect on the discharge of typhoid bacilli.

In concluding this section we have to deplore the fact that so far the attempts to cure intestinal carriers have not yielded results affording convincing evidence of their success. It must, indeed, be admitted, on consideration of all the evidence adduced by the surgeon and the pathologist as to the nature of the lesions met with in carriers, that the problem of effecting a cure in these carriers is an extremely difficult one. In the case of carriers who are in an early stage of this condition, there may be some hope of effecting a permanent cure by one or other of the methods already tried and quoted above, but in long-standing chronic cases the prospect of success of this kind would seem to be extremely remote.

Though it may prove impossible to render the chronic carrier typhoid-free, the prospect of diminishing the output of carriers by some modification of the régime employed in the treatment of enteric cases is more hopeful. G. Mayer's (1910) observations led him to believe that an exclusive milk diet during the disease, and an abundance of milk during convalescence, were most favourable in diminishing the crop of carriers. With a mixed diet, on the other hand, the carrier state was more likely to supervene. The data on which he founded this opinion (which is supported by Drigalski) were not, however, sufficiently extensive to admit of reliable conclusions being drawn. Tsuzuki and Ishida (1910) recommend the use of arsenic and iodide of potassium in convalescent typhoid cases, and claim that the bacilli leave the excreta at a somewhat earlier period under such treatment. Groups of convalescents were examined who had been free from fever for two to three weeks.

One group of twenty-nine cases received potassium iodide in doses of 0·5 to 1·0 gramme t.d.s.; another group of twenty-one cases received arsenic in the form of Fowler's solution; while a third group of sixteen cases received no special medicinal treatment. The result was that in those treated with arsenic the bacilli disappeared in thirty-four days on an average; in those treated with the iodide of potassium the bacilli disappeared in forty-two days on an average; while in the untreated the bacilli took fifty-nine days on an average to disappear from the excreta. Such a result cannot be considered more than encouraging, but the development of chemo-therapeutic lines of treatment in bacterial infections may possibly lead to a solution of the problem of rendering the carrier typhoid-free.

URINARY CARRIERS.

Pathogenesis of the Condition, and Treatment.

In the course of investigations on the carrier problem, urinary carriers have been met with much less frequently than intestinal carriers. The great majority of the chronic carriers discovered in connection with endemic typhoid fever have been passing the typhoid bacillus in the fæces only, and not in the urine. Certainly the typhoid bacillus is occasionally found in the urine of chronic intestinal carriers, especially of the female sex, but in these cases their presence in the urine is almost certainly due to fæcal contamination of the urine. When catheter specimens have been taken (in a few instances recorded), the urine has been invariably free from typhoid bacilli.

In chronic intestinal carriers of the male sex I have never found the urine positive.

Though in chronic intestinal carriers the occurrence of typhoid bacilli in the urine is rare, it is not so uncommon to find both fæces and urine infective in the acute or transitory carriers and in early convalescent carriers. In this connection reference may be made to the data regarding transitory carriers in Scheller's milk-spread epidemic. Some of these passed typhoid bacilli in the fæces only, some in the urine only, and some in both fæces and urine. In such cases one may suppose that there is a transient typhoidal septicæmia.

The true urinary carrier passes the typhoid bacillus in the urine only, and it is fortunate that such cases are so infrequently met with, as the danger of spreading infection by the urine is much greater than in the case of intestinal carriers.

The earliest cases of this condition were reported about the same time by Rousing (1898), Houston (1899), and Young (1900). It will be advisable to give an account of some of these cases in detail, as they tend to throw some light on the pathogenesis of the condition.

Rousing's case was a male of fifty-three years, who had had enteric fever eighteen months previously. During the primary attack there had been no retention of urine and no necessity for catheterization. In convalescence the urine was milky, and on standing, a heavy deposit formed. Several months later he began to have vesical pain and frequency of micturition, especially at night. The urine was acid and contained pus, but no blood.

The typhoid bacillus was present in large numbers in the urine. A suprapubic cystotomy was performed, and the mucosa was found to have a dark red colour, with numerous ulcerations separated by swollen rugæ. Cloudy urine came from both ureters. The patient died one month after operation. At the autopsy the right kidney was enlarged, and small abscesses were scattered about the kidney substance. The pelvis contained a stone of the size of a walnut, and the pelvic mucosa was also swollen and ulcerated. The left kidney was in a similar but less marked condition, with millet-seed abscesses in the cortex, but no stone. There was no evidence of tubercle. Rousing believed that the calculus had been present for some time before the attack of typhoid fever, and that the trauma caused by it determined the localization of the *B. typhosus* in the kidney.

It is known that some cases of nephrotyphoid may be associated with focal abscesses in the kidneys, but they are rare (*vide* Flexner, 1896).

Houston's case was a female of thirty-five years, who presented no definite evidence of a primary typhoid infection. Three years before coming under observation she had been living in a house where two children died, one of bronchitis and the other of diarrhœa (patient's diagnosis). She had helped to nurse these children. Shortly afterwards she suffered from frequent micturition, which latterly was accompanied by pain.

In 1895 (December) she had gone to hospital, where she was treated for three months for painful and frequent micturition and occasional passage of blood. She returned to work, but in May, 1898, she again consulted a doctor, who, after treating her for cystitis, sent her to hospital, where her condition was thoroughly investigated. Her urine was turbid and opalescent, strongly acid, and contained a small amount of albumin. The sediment contained numerous squamous cells with pus cells and bacteria. The typhoid bacillus was repeatedly recovered from the urine.

Her serum also agglutinated a known strain of the typhoid bacillus in a dilution of 1 in 100. She remained in hospital for six weeks without showing any abnormal temperature or other symptoms pointing to typhoid fever.

It was from this case that Houston drew the important conclusion that typhoid fever is a true general infection, and not merely of local origin in the Peyer's patches of the intestines. This view was elaborated more fully by Horton-Smith (1900) in his Goulstonian Lectures of the following year. This author held that the mesenteric glands are the primary seat of the typhoid infection, a view which by several years anticipated that of Forster. (See also Levy and Gaehtgens, 1908.) With regard to the presence of the typhoid bacillus in the urine of typhoid patients, Horton-Smith found positive results in 25 per cent. of cases examined. This is the percentage found in most recent work on the subject of typhoid bacilluria. Of 289 post mortems in St. Bartholomew's Hospital on typhoid patients (during thirty years), Horton-Smith notes that abscesses of the kidney occurred only once. He believed that the typhoid bacillus grew in the bladder, the walls of which were chronically inflamed.

Young's case (also reported by Gwyn, 1899) was a male of thirty-nine years who had had typhoid fever in 1893. On admission to hospital at that time he had shown pyuria, and one of his complaints was pain during micturition. Ten days after defervescence a relapse occurred, but the pyuria continued. In 1897 the urine was very purulent, and the *B. typhosus* was first isolated from it in 1898. His serum gave a positive Widal reaction.

In January, 1900, he returned to hospital, when the urine was again positive. By cystoscopic examination a chronic ulcerative cystitis was found. There was also a secondary infection with the gonococcus, both gonococci and typhoid bacilli being isolated from the bladder. The fact that this patient also had syphilis in 1889 may have had some influence in predisposing the genito-urinary tract to particular and prolonged infection by the typhoid bacillus.

I have already referred to the cases of Irwin and Houston and Niepratschk, both of which were responsible for fresh cases of typhoid in their vicinity.

Greaves (1907) reported the occurrence of a typhoidal pyonephrosis in a patient of thirty-six years, who had had his primary attack of enteric six years previously. From the pain during micturition and the swelling in the left renal region a diagnosis of renal trouble was made, and cystoscopic examination revealed that the left kidney was not functionating. At operation a pyonephrosis was found, with a phosphatic calculus in the left ureter. From the pus the typhoid bacillus was recovered in pure culture. Fourteen days after the operation the patient's blood-serum agglutinated the typhoid bacillus in a dilution of 1 in 200.

Another important urinary case also associated with pyonephrosis, and treated surgically with success, was reported by Adrian (1908), and also more fully by Meyer and Ahreiner (1909). The patient was a girl who in 1897 (when six years of age) suffered from pyonephrosis. While under treatment in hospital for this condition she contracted typhoid fever, the pyonephrosis apparently antedating the typhoid attack. Shortly after her discharge home she infected a brother and both her parents with typhoid fever. For ten years the girl remained perfectly well. Then gradually she began to suffer from acute pains in the left kidney region, with swelling of left side of abdomen and thighs, and cloudy urine. A communication had evidently been established between the sac and the bladder, so that the typhoid bacilli vegetating in the sac were continually being discharged by the urine. In July, 1907, nephrectomy was performed. Typhoid bacilli were present in pure culture in the purulent contents of the sac. The actual seat of vegetation had very probably been an ulcerated area which was found near the ureteral orifice. Eight days after the operation bacilli were found in the urine, but afterwards it remained quite free of typhoid bacilli. Before operation the patient had given a Widal reaction of 1 in 10,000, but after operation the titre fell to 1 in 150.

These urinary cases bear a strong analogy to the gall-bladder cases, and therefore one would require to exercise the same caution in judging of the effect of operation. The absence of typhoid bacilli in the urine in the above case after operation certainly suggests that there were no secondary depots in the bladder itself, as one would have expected in such a chronic condition.

Sufficient data have not yet accumulated with regard to the organic lesions associated with the urinary carrier state to enable us to formulate lines of treatment applicable to particular cases. It would be well, however, whenever opportunity offers, to examine these cases with peculiar care, employing the modern methods of cystoscopy and ureteroscopy, so that the sum total of definite knowledge on this subject may be increased.

That the principal depot of the *B. typhosus* may be a chronically inflamed or cystic renal pelvis is known, and this may or may not be associated with secondary depots in an inflamed bladder.

It is not yet possible to state whether the pathological findings met with in urinary carriers bear any relation to the lesions associated with cases of so-called "nephro-typhoid," or of acute typhoidal cystitis with definite bladder lesions. On this latter subject the articles of Schuder (1901) and Schaedel (1906) may be consulted. With regard to the kidney, Cagnetto and Zancan (1907) have shown that, in most cases of typhoid fever, inflammatory foci (so-called "lymphomata") with focal necroses, or even minute abscesses, are found. Whether such foci may act as vegetation depots of the typhoid bacillus in urinary carriers is as yet uncertain. It is more likely, as has been suggested by Pick (1910), that in the urinary carrier the bacilli lie in nests situated in recesses of the urinary tract—*e.g.*, diverticula of bladder or kidney pelvis, intraurethral and paraurethral ducts in the female, and prostatic ampullæ and vesiculæ seminales in the male. Pick examined these organs in thirty-two autopsies of typhoid cases, and in two instances discovered a suppurative spermatocystitis and prostatitis due only to the *B. typhosus*. The testes and epididymes were not involved.

Treatment of Urinary Carriers.

Urotropin has proved so valuable in the bacillurias occurring during typhoid fever and in early convalescence from that disease that one naturally anticipated a similar efficiency in urinary carriers. Such hopes have not been realized so far as the recorded reports show, and perhaps the reason of its failure is to be sought in the chronically inflamed and rugose state of the bladder, which may render the typhoid bacillus less readily accessible to its influence. Urotropin certainly has a marked temporary effect in reducing the number of bacilli excreted, but the latter return in full force when the administration of the drug is suspended.

The treatment adopted by Niepratschk (*vide* p. 57) in his case is so instructive that I give it in detail.

The carrier was isolated on February 23, 1908, and treatment with urotropin was at once begun.

First Course of Urotropin.—February 23, 1908: Received 1 gramme. February 24 to March 8: Received 2 grammes daily.

Result: Soon after the commencement of the treatment the urine became clear and the number of bacilli decreased. On February 26 the urine contained only 10,000 bacilli per c.c., and on February 28 none. On March 17, when the remedy had been stopped for seven days, the bacilli were as numerous as ever.

Second Course.—March 17 to 24: Received 3 grammes daily (=24 grammes in all), and a further 11 grammes up to April 6.

Urotropin was then laid aside, and hetralin—a compound containing 56 per cent. urotropin and 44 per cent. resorcin—was tried.

Hetralin Course.—April 15 to 18: Received 2 grammes daily. April 19 to May 16: Received 3 grammes daily. May 17 to June 24: Received 5 grammes daily. June 25 to July 2: Received 6 grammes daily. July 3 to 11: Received 8 grammes daily.

The carrier's health was not affected by the drug. His appetite remained good. A reduction in the number of bacilli resulted, but it was not permanent.

Borovertin, a compound containing urotropin and boric acid (=hexamethylen tetramin triborate), was finally tried, with apparent success.

Borovertin Course.—July 23 to August 27: Received 6 grammes daily (=1 gramme six times a day, and later 1·5 grammes four times a day).

This drug was not so well tolerated as the others. The patient suffered from loss of appetite and weakness, and his body-weight fell from 81 kilos to 70 kilos during the short period from August 1 to 29. The drug was therefore stopped, and the patient recovered very quickly. The disinfectant action on the urine was, however, remarkable. Two days after the first dose bacilli were still present in considerable quantities, but thereafter none could be demonstrated by repeated examinations. Examinations on July 27, July 31, August 3, and many following days, were negative. On October 23 a litre of the urine was treated by the precipitation method employed in searching for *B. typhosus* in water, but the result was negative. As large a quantity as 2 litres was also examined without result.

On November 1, 1908, Sergeant B. was considered "cured," and resumed his regimental duties. Weekly or biweekly examinations of his urine were still continued, but all were negative, and Niepratschk, writing in December, 1909, says that no further cases of typhoid fever have occurred in Sergeant B.'s regiment, although he occupies his old position in the barracks.

What impresses one in the recital of this case is rather the systematic and persistent method which was adopted than the ultimate result. If this case may be chronicled as a "cure," it is a remarkable testimony to the efficacy of the drug treatment, that a carrier of such long standing, presenting in all likelihood lesions of a chronic character in his urinary tract, should be so completely restored to a normal condition. Any further data regarding the after-history of Sergeant B. will be welcomed. In the meantime it may be said that borovertin, either alone or—perhaps preferably—after a preliminary course of urotropin, should be given a trial in urinary carriers.

Another cure by borovertin has been reported by Ustvedt (1910), but I have been unable to secure full details of the case. The carrier was a ship steward, who continually excreted typhoid bacilli in his urine. After a six weeks' course of borovertin (120 grammes altogether) the bacilli disappeared.

I now come to the treatment adopted by Irwin and Houston (*loc. cit.*) in their female carrier case (*vide* p. 35).

For the first five weeks tonics and urinary antiseptics were tried, but with no effect on the bacilluria. Headaches and gastric pain were still complained of. Vaccine treatment was then resorted to, the homologous strain being employed in the preparation of the vaccine.

Course of Vaccine Treatment.—August 25, 50,000,000 : urine positive on September 1. September 2, 100,000,000 : urine positive, but bacilli less numerous, on September 16. September 20, 200,000,000 : urine positive on September 22 ; bacilli as numerous as ever.

The patient was now put on sodium lactate, and the urine made alkaline.

Urine negative on October 8. October 9, 300,000,000 : urine negative on October 20. October 23, 500,000,000 : urine negative on October 24 ; clear, with no pus and no albumin ; urine and fæces negative on November 21. November 21, 1,000,000,000 : urine negative on November 23 ; fæces negative.

During the treatment the headaches, gastric pain, and feeling of tiredness, disappeared, and the patient gained markedly in weight. The last examination, which was negative, was made on April 24, 1909 (Houston, 1909).

The authors believed that by rendering the urine alkaline the typhoid bacilli became more susceptible to the action of the immune bodies developed in the serum by the vaccinations.

The observations on the female urinary carrier reported by Walker Hall and Roberts (see p. 36) are of considerable interest. For fifteen months daily examinations of her excreta were made, and on two occasions only did the organisms appear in the fæces. In January, 1909, the urine was positive, but in April the bacilli disappeared from the urine, and were absent until January, 1910. There was thus a latent period of nine months, and it was thought that the focus had been exterminated as the result of the vaccine treatment which was started in April, 1909. The vaccine treatment was continued for five months, doses rising from 50,000 to 1,000,000,000, being given at intervals of five days. The writer is greatly indebted to Professor Walker Hall for permission to publish the following additional notes respecting the case. In a personal communication (March, 1912), Professor Walker Hall states that, after unsuccessful courses of urotropine and autogenous vaccines, the urine was collected by segregation methods on several occasions, with the result that the right ureter yielded urine containing typhoid bacilli, together with evidences of renal lesions, while the left ureteral urine was free from both. The patient consented to an examination of the kidney itself, with permission to remove it if necessary. At the operation, which was carried out by Mr. C. F. Walters, the kidney was found to be in a healthy condition, except for several aggregations of minute calculi. These were removed as far as possible, and it was decided to sew the kidney together and return it to its place.

The recovery was uneventful, except that after twenty-four hours the temperature rose, and there appeared the symptoms of a typhoid septicæmia. This disappeared in two days. The calculi on examination contained organic material, with a small amount of phosphates, and the *B. typhosus* was recovered from them in pure culture. For some time a small number of organisms appeared in the urine every day, along with a small amount of pus. A course of borovertin was then tried for three months. This diminished the organisms in the urine, but did not remove them entirely. The next procedure was to grow the organisms on the patient's blood for some weeks. A vaccine was then made, and injected in doses rising to 6,000,000,000. When this amount was reached, the bacilli disappeared from the urine, and during the past four months (up to March, 1912) the urine has been typhoid-free. Examinations are to be continued throughout the present year.

Two chronic urinary carriers, invalided from the Indian army, have been treated with typhoid vaccines (Fawcus, Kennedy and Cummins, 1910) in this country, but no definite improvement in their condition was realized. These cases had previously been treated with urotropin without effect, but it was noted that when a diuretic ("sanmetto") was given in combination with the urotropin, a marked fall in the bacilluria took place, and the purulent deposit became almost nil. On cessation of the treatment, however, the bacilli were discharged again in large numbers. Major Cummins suggests that more definite results might be attained by combining sanmetto and urotropin with vaccine treatment; but in the light of Niepratschk's results it may be contended that it is the persistent pushing of treatment over a prolonged period that is most likely to be of value in the end.

Diagnostic Methods employed in the Search for Carriers.

The demonstration of the typhoid bacillus either in the fæces or in the urine is essential before a person can definitely be certified to be a carrier.

In dealing with large institutions, however, where enteric fever has been endemic, some indication may be got of the presence of carriers by performing an extensive series of Widal tests, commencing with those subjects who are ascertained to have suffered from typhoid fever in previous years, or who may happen to present symptoms of gall-stone trouble.

It is stated by Kayser (1909) that about 75 per cent. of carriers give a well-marked Widal reaction, but I am inclined to think that this percentage is rather high, if agglutination at 1 in 100 be taken as the criterion of a positive Widal reaction. Of nine chronic carriers whom I have personally observed, five gave a definitely positive reaction, while four gave an incomplete or absolutely negative reaction. On the other hand, in institutions, a positive reaction is occasionally obtained in persons whose fæces, though repeatedly examined, fail to show the presence of the typhoid bacillus. Certainly in such cases we have to reckon with intermittent periods, imperfect bacteriological methods, and possibly other factors not yet fully understood. Kamm (1909) had an experience of the Widal test which was unfortunate, and perhaps exceptional. He commenced the search for carriers in an asylum by the examination of 136 blood-samples. Four of these gave a reaction of 1 in 50, one gave a reaction of 1 in 100, and three gave a reaction of 1 in 200. Of these eight persons, four had had enteric fever about eight or twelve years previously, while in the other four there was no record of typhoid. Castor-oil was given to these eight persons, and their fæces repeatedly examined thereafter, but in none of them could the typhoid bacillus be demonstrated. It would be interesting to know the further history of these cases, and whether definite carriers were ultimately discovered.

Eccard (1910), in the course of his examination of an asylum (*vide* writer's Report, p. 60), commenced by performing Widal tests in all departments of the building. The figures obtained he does not record, but he was able to classify the inmates into three groups :

1. Those who gave no Widal reaction.
2. Those with Widal reaction of 1 in 50.
3. A smaller number who almost always gave a reaction of 1 in 100. The stools of this group were frequently examined, and in five of them he was able to demonstrate the typhoid bacillus. In three others of this group who frequently gave a reaction of 1 in 100, he could never demonstrate typhoid bacilli in the fæces.

An important point noted by him in the course of this investigation was that in a large number of those who were Widal-free, or who occasionally gave a reaction in 1 in 50, the titre would suddenly spring to 1 in 100, with symptoms of intestinal disturbance, vomiting, and diarrhœa. After the attack the titre again fell.

Some trouble was experienced with three severe tubercular cases who gave positive Widal reactions. One of these died, but there were no signs of typhoid fever. (He makes no mention of the condition of the gall-bladder.) This question of positive Widal reaction in cases of tubercle is discussed on p. 113.

Eccard, however, thinks that, at least as a preliminary step, the Widal test should be employed in large institutions, a titre of 1 in 50 to be regarded with caution, and one of 1 in 100 as suspicious. He does not appear to have met with carriers who give practically no reaction even in 1 in 20.

When proper bacteriological conveniences are available, the best method of procedure is the immediate examination of the excreta of all persons concerned, commencing with those who give some history of having passed through a typhoid attack, or who suffer from gall-stones, and then passing on to the others. At the same time Widal tests should be carried out, and repeated bacteriological examinations made at intervals, in those cases which give a positive Widal reaction.

It is impossible here to describe in detail the various media employed or recommended for the isolation of the typhoid bacillus from the excreta. For those interested in this subject a list of these media will be found at the end of this section.

Amidst a plethora of methods and modifications of methods, all of which are probably excellent in the hands of those accustomed to them, it seems to me of far more importance to obtain a thorough knowledge of the potentialities and the working efficiency of one medium than to be continually changing from one medium to another without a clear knowledge of the advantages to be derived by the change. Many of the newer media introduced for the isolation of the typhoid bacillus have been recommended strongly on their merits as inhibitors of the *B. coli* group, but the data on which such judgments are based have usually been obtained by practice with artificial mixtures of *B. typhosus* and *B. coli*, to which the particular medium or inhibiting agent in the medium is added, and not with the actual fæces of typhoid patients or carriers. The writer's experience has been confined to the bile-salt-lactose-agar medium of MacConkey (1901), with neutral red as indicator. This medium has been in constant use for many years, and has proved eminently satisfactory. The actual method is, briefly, as follows:

For Fæces.—About two to three large loopfuls of the fæces are emulsified in broth, and allowed to sediment for an hour. From the upper portion of the fluid two small loopfuls are removed, and spread by means of a bent glass rod over two or three Petri plates, containing the solidified medium, which should be quite dry. On the following day colourless colonies, suggesting the typhoid bacillus, are picked off and inoculated into mannite-peptone-water. If acid only is formed in any tube or tubes, and no gas, the probability is strong that the organism is the typhoid bacillus (or the dysentery bacillus—Flexner type), but it must be remembered that the fæces contain a small group of organisms whose characters in some particulars present a strong similarity to those of the *B. typhosus* (Morgan and Ledingham, 1909). As a rule these organisms give little trouble, and can be readily differentiated by the application of fermentation and agglutination tests.

The *B. typhosus* gives an acid reaction without gas formation on glucose, mannite, and sorbite; a late acid reaction on dulcite (Penfold, 1910; Grattan, 1910); and no reaction on cane-sugar or lactose. Indol is tested for by Ehrlich's method (*vide* Marshal, 1907) after four days' growth on broth, and finally an agglutination test is made with a potent antityphoid serum which agglutinates a known strain up to 10,000 or 20,000.

Some workers commence the investigation of a suspicious colony by performing an agglutination test, but it frequently happens that typhoid bacilli taken directly off the plate, and tested with an antiserum, give a very feeble and unconvincing reaction. Scheller (1908) has observed quite a gradation of agglutinability in typhoid colonies taken directly from the same plate. Media containing certain inhibiting agents, like malachite green, have been found to reduce the agglutinability of typhoid bacilli when examined directly.

By performing the agglutination test after subculture on broth, all the strains which I have isolated from MacConkey plates (either from fæces or urine) have without exception agglutinated up to 1 in 5,000 or 1 in 10,000.

Further, by preliminary performance of the fermentation tests one acquires a knowledge of the characters of the many members of the non-lactose group, whose appearance on plates may simulate strongly that of the typhoid colony, which may, indeed, give a slight reaction with a potent antityphoid serum, but which can be absolutely excluded by their fermentation and other properties.

A motile non-lactose-fermenting organism producing a permanent acidity on litmus milk and no indol, rendering glucose, mannite, and sorbite, but not cane-sugar, acid, has invariably satisfied the agglutination test when finally applied. The rare occurrence of a non-motile or temporarily non-motile typhoid strain has been reported on at least two or three occasions. Those recorded recently by Ernst (1908) and Fischer (1909) ultimately recovered their motility after cultivation on various media. Such a strain I have also encountered on one occasion. It gave all the fermentation tests and the agglutination and absorption tests, but, in spite of various methods of culture and animal passage, it has not so far given evidence of motility. The strain referred to was obtained from the stools of a female lunatic in the course of investigations in an asylum. Further samples of fæces were negative, and it seems quite possible that this woman had been a so-called "temporary" or "acute" carrier.

It has already been mentioned that frequently the stools of typhoid carriers give practically pure growths of *B. typhosus* on plates, and there is little trouble, therefore, in isolating them in such circumstances. I have not observed that on these occasions the stools are unusually loose in character, but, on the other hand, there seems to be no doubt that after a period of constipation it may be possible to encourage the appearance of the bacillus in the fæces by the administration of a mild purgative or cholagogue.

The isolation of *B. typhosus* from the urine in urinary carriers is as a rule very easy, as it is generally the only organism present. Some difficulty is said to have been encountered in getting organisms isolated from urine to agglutinate properly, but this has not been my experience.

The diagnosis of carrier cases by serological methods (opsonins or tropins, or complement-deviating bodies) can only be regarded as adjuvants to the ordinary bacteriological routine. This subject will be discussed later (*vide* p. 125).

Finally I may refer to an interesting, though not very practical, method of demonstrating the presence of *B. typhosus* in a carrier who may not at the time be actively shedding the bacillus in the fæces. Weber (1908) passed a dose of oil (about 200 c.c.) into the stomach, thereby causing a regurgitation of typhoid-containing bile into that organ. After half an hour the stomach was emptied, and a fluid obtained which presented an upper oily layer and a lower watery bile-stained layer. In two chronic carriers whose stools contained only a very few typhoid bacilli, he was able to recover the typhoid bacillus from the upper oily layer. It is not always possible, however, to obtain this backflow of bile into the stomach.

Media employed for the Isolation of B. Typhosus from the Excreta.

It would take too much space to discuss the respective merits of the many media employed for this purpose, nor can reference be made here to the results recorded by those who have had personal experience of their use, or who have instituted comparative tests as to their efficiency. For the preparation of the various media the reader is referred to the original papers (see Bibliography).

Only those media which are in current use at the present time will be referred to.

1. Bile-salt-lactose-neutral-red-agar.

MacConkey's (1901) original media did not contain the neutral-red. The latter was added on the suggestion of Grünbaum and Hume (1902). For full information regarding the development of bile-salt media, the reader is referred to a communication by MacConkey (1908), in which the exact mode of preparation is described.

2. Medium of Drigalski and Conradi (1902). Lactose-litmus-nutrose-kristalviolett-agar.

The preparation of this well-known medium is described in most bacteriological textbooks. On the Continent its use is now very largely superseded by media of more recent development (see below).

3. Medium of Endo (1903). Lactose-fuchsin-sodium-sulphite-agar.

4. Method of preliminary enrichment by caffeine. Roth (1903), Ficker and Hoffmann (1904), Lubenau (1907), Werbitzki (1909).

The fæcal material is incubated in the caffeine-enriching solution, and finally plated on Drigalski-Conradi plates.

Caffeine has also been added with advantage to fuchsin media (Gaehtgens, 1905) and malachite-green media (see below).

5. Media containing malachite green, introduced by Loeffler (1903), and since modified and improved by himself and others:

(*a*) Malachite-green-nutrose-agar. Loeffler (1906).

(*b*) Malachite-green-bile-agar. Loeffler (1907).

(*c*) Malachite-green-sodium-sulphite-bile-agar. Padlewski (1908).

(*d*) Malachite-green-safranin-reinblau media. Loeffler, Walter, Dibbelt, and Wehrlin (1909).

Modification by Dennemark (1911), who employs decolorized reinblau.

(*e*) Method of Lentz and Tietz (1903, 1905), in which the malachite-green medium is used mainly as an enriching medium, the growth being subsequently plated on Drigalski-Conradi or Endo plates. This is the method in current use at the Strassburg Institute.

6. Brilliant-green-picric-acid-agar. Medium of Conradi (1908).

Fawcus (1909) has modified this medium by adding to it bile salt and lactose.

7. China-green-agar. Medium of Werbitzki (1909), McWeeney (1910). Combined Endo and China green. Schröder (1910).

8. China-blue-malachite-green-agar. Bitter (1911).

9. Rosolic-acid-lactose-blood-agar. Mandelbaum (1912).

Detection of B. Typhosus on Plates by Complement Fixation.

H. R. Dean (1910) has shown that it is possible to detect the presence of typhoid antigen on mixed plates by complement fixation experiments with extracts of the washed-off growth and a specific antityphoid serum. For the exact technique the original paper should be consulted. Eighty-five plates of mixed growth from fæces of actual or suspected typhoid carriers were examined by this method, and in eighty-one cases the result was in agreement with the cultural findings. The presence of even half a normal loop of *B. typhosus* added to the washed-off growth of *B. coli* incubated for forty-eight hours at 37° C. on a Petri plate could readily be detected by this method.

During the last two years some important comparative trials have been made of these various media, but, as might have been expected, the results have shown little unanimity. It would appear, indeed, that the media which prove most efficient in these trials are those with which the various authors themselves have had most practical experience. The results certainly bear out the statement made earlier in this section, that a thorough knowledge of the capabilities of these media under all conditions is essential before one can arrange them in an "efficiency scale." For an account of these trials the reader is referred to the writer's Local Government Board Report (pp. 103, 104, 105).

Discussion of the General Question of Carrier Infectivity.

This question involves the consideration of many factors which must play a part in the successful infection of a new host by a carrier. In the first place, the bacillus has to be transferred directly or indirectly from the carrier to the new host. The degree of likelihood of this transference taking place will depend, perhaps largely, on the personal hygiene of the carrier and the measures of disinfection adopted by him, provided he is cognizant of his condition, and on the method of disposal of his stools and urine. Where the carrier is unaware of his condition, the chances of successful transference are much greater, in spite of average personal hygiene, and they are also very much intensified in the case of lunatics of unclean habits. Further, much will depend on the environment and personal hygiene of the new host, in so far as these conditions affect his liability to exposure to infection. If these conditions are satisfied—*i.e.*, given carriers and associates of uncleanly personal habits—the probability of successful transference to a new host is greatly enhanced, provided the carrier is actively excreting the typhoid bacillus. In these pages numerous instances of prolonged intermission (up to two years in some cases) are referred to. Certainly, some of these may be only apparent intermissions—*i.e.*, the bacilli discharged may be so few that our bacteriological methods cannot reveal them. There can be no question that many of the instances of intermittent infectivity cited in previous sections are to be explained by a variation in the numbers of bacilli excreted by the carrier from time to time. Obviously, the more numerous the bacilli excreted are, the greater is the chance of their being successfully transferred to a new host.

The magnitude of the dose received by the new host is probably a most important factor in determining whether a subsequent infection takes place or not.

Given a successful transference to the new host, there remain for successful infection at least two further factors—viz., virulence of the strain and the individual susceptibility of the new host. With regard to the first, a general notion has prevailed that carrier strains are less virulent than those from acute typhoid cases. As to this there is no sufficient evidence. If, as some authors have done, we take the mortality among the affected as the criterion of virulence, we find entirely discordant conclusions. If, on the other hand, the effect of the *B. typhosus* on animals be selected as an index of its virulence, the evidence hitherto available on this point is found to be inconclusive. As a matter of fact, seeing that the experimental reproduction of enteric fever in animals is impossible, we possess really no reasonably certain experimental criterion of virulence. Intraperitoneal inoculation of the guinea-pig has, however, been widely employed in testing the virulence of typhoid strains, and the variations in the magnitude of the minimal lethal dose for that animal have been shown to bear some relation to the ease with which the bacillus is acted upon by the various antibodies in normal and immune serum (lysins and opsonins).

So far as carrier strains have hitherto been compared with those isolated from typhoid cases in respect to their virulence for the guinea-pig, no marked divergence has been found. The same variations in virulence are met with among carrier strains as among those from acute cases.

Lentz (1905) sent twenty carrier strains to the Institut für Infektionskrankheiten to be tested for virulence, with the result that neither a greater nor a less degree of virulence than that of ordinary typhoid strains could be detected. It cannot be said, however, that enough strains have yet been examined in this respect to justify a definite decision on the matter. Most authors have omitted to test the strains they have isolated on the guinea-pig. It is highly important that, in performing such tests, as small an interval as possible should elapse between isolation of the strain and the determination of its virulence. I have adopted the following technique in testing the virulence of carrier strains for the guinea-pig.

The fæces are plated in the usual way, and on the following day, if typhoid-like colonies are present, one is touched with the point of a straight needle, and inoculated into a fixed quantity of broth (6 c.c.), which is then incubated for forty-eight hours. A control mannite tube from the same colony is also inoculated, so as to make certain that the colony is really a typhoid colony. Growth for forty-eight hours in this way gives a fairly constant number of bacteria per c.c. (700,000,000 to 800,000,000). Guinea-pigs of 250 grammes weight are then inoculated intraperitoneally with falling quantities of the broth culture. The result has been that most of the strains tested kill in 1 c.c., a few in 0·1 c.c., and a few in 2 c.c. There is therefore no evidence of lack of virulence.

Far more important than the isolated virulence test is the periodical test, as there is certainly the possibility that the virulence of the strain may vary at different times of the year in the same carrier. My observations on this point are not on a sufficiently large scale to permit of trustworthy conclusions being drawn, but some results already obtained suggest that some such variation in virulence occurs. For example, a strain isolated from an intestinal carrier on October 23, 1909, killed in $\frac{1}{10}$ c.c. A culture isolated on November 19 killed only in 1 c.c. On February 1, 1910, the culture isolated did not cause death in 1 c.c. On February 14 it did not kill in 2 c.c.

However, without much further investigation it would be unjustifiable to assume that the virulence of a carrier strain is much reduced during the winter months. Whether the guinea-pig's susceptibility to the *B. typhosus* varies in the opposite direction according to the season must be left undecided.

That an avirulent bacillus might suddenly regain its virulence was suggested also by Scheller (1909), who, however, gave no evidence in support of this point.

Niepratschk (1909), who made a very careful examination of the strain isolated from the urine of a urinary carrier (see p. 59), found that its virulence for the guinea-pig was distinctly low. By passage through the guinea-pig he succeeded in raising the virulence considerably, and he suggested that a similar increase of virulence might be attained by passage through the human body, and in this way slight or unrecognized infections might be followed by infections of average severity.

That laboratory infections may occur by direct ingestion of carrier strains is shown by an observation of Bolduan and Noble (*loc. cit.*) in the course of their investigation of a carrier who had contaminated a milk-supply (see p. 50). A female laboratory assistant accidentally drew into her mouth, during pipetting, a small quantity of a broth culture of the carrier strain. Two weeks later she developed typhoid fever, which ran a typical course, ending in recovery. A blood-culture taken during the course of the disease yielded typical typhoid bacilli.

I now come to the second factor involved in the successful infection of a new host by a carrier—viz., the susceptibility of the host. Unfortunately, we have no satisfactory method of experimentally estimating the strength of this factor, and our conception of its importance must depend for some time on actual observed facts. Thus we have seen that the typhoid bacillus may be taken into the intestine, may even gain entrance to the general circulation and be passed in the urine, without giving rise to any obvious infection at the time. Scheller's (1908) cases in the milk-spread epidemic already quoted (*vide* p. 47) afford one of the most convincing instances of this phenomenon. In view, however, of the demonstration of typhoid bacilli in the fæces and blood during the incubation stage of typhoid fever, by Mayer, Conradi, and others, it might be expected that some of these so-called " temporary carriers " would ultimately present symptoms of infection, and Mayer (1910) has actually observed such cases.

It seems appropriate here to refer to certain observations of Busse (1908) on the occurrence of typhoid bacilli in the blood of patients at whose autopsy tubercular lesions only were found.

The first case was a female of forty-eight years who was suspected to be suffering from typhoid fever. She was admitted to hospital on January 31, 1907. The typhoid bacillus was twice isolated from the blood—viz., on February 1 and 6, 1907—but the serum gave a negative Widal reaction. Death took place on February 7, 1907. At the post mortem most of the organs showed miliary tubercles, the lymph glands were caseous, but no lesions pointing to a typhoid infection were detected (Peyer's patches not swollen). The organs, however, were not examined bacteriologically, and no mention is made of the condition of the gall-bladder. Further, what appears to me a point of importance was the fact that rose-spots were present on the fourth day of her sojourn in hospital. There was no evidence of her having had a previous attack of enteric fever. The second case was also a female, aged twenty-five years, suspected to be suffering from typhoid fever, who was admitted to hospital on April 9, 1907. The Widal reaction was negative, but the typhoid bacillus was isolated from the blood on April 10, 1907. The spleen was palpable under the ribs, and apparently also tender. Death took place on April 16, 1907. At the autopsy generalized tuberculous lesions were present in the lungs, intestine, peritoneum, etc. There was no swelling of the Peyer's patches, but three ulcers with tuberculous areas at their bases were present in the small intestine. The spleen, lungs, liver, bile, and mesenteric glands, were bacteriologically examined, with negative results. A typhoid-like bacillus was, however, isolated from the bile, but it was not thoroughly examined, which is unfortunate.

In Busse's view, the typhoid bacillus was living a saprophytic existence in these two cases, just as in those carriers who have never had any clinical symptoms of a typhoid infection. The blood-invasion, he believed, was brought about by an increased permeability of the intestinal wall, owing to the tuberculous lesions therein. A phthisical female patient in whom there was no suspicion of typhoid fever was also examined. From her blood the typhoid bacillus was isolated on several occasions, although the Widal reaction proved negative. The urine and fæces of this case were examined bacteriologically, with negative results.

Further, from the blood of a case of pneumonia the typhoid bacillus was isolated, although the urine and fæces were negative. This patient presented symptoms of diarrhœa at first, but the course of the illness proceeded as a typical pneumonia of the right lower lobe. No evidence is afforded, however, proving that the lung infection was not of a typhoidal nature.

Busse's conclusion was that all these cases were probably carriers, although they presented no history of having had typhoid fever. The typhoid bacillus, leading a saprophytic existence in the intestine, reached the blood-stream as a result of an increased permeability of the intestinal mucosa due to the tubercular lesions. Further, he concluded that the presence of typhoid bacilli in the blood is not an absolute sign of the presence of a typhoid infection.

These results of Busse have to be considered in the light of accumulated knowledge regarding atypical and apparently symptomless enteric fever on the one hand, and typhoid carriers with no typhoid history on the other hand. The explanation given by Busse, that these cases were really typhoid-carriers, and that a passive invasion of the blood-stream took place as the result of the intestinal lesions, may be a perfectly sound one, but there is nothing in the evidence which entirely excludes the possibility of these cases being really mixed infections of tubercle and typhoid.

In chronic carriers the blood has very seldom been examined bacteriologically, but in the few examinations made, it has invariably been negative. During an exacerbation of cholecystitis, however, the blood may be found to contain the bacilli.

Some years before Busse's observations on this question appeared, Jurgens (1907) had reported the finding of typhoid bacilli in the fæces of a tuberculous patient in the course of an epidemic of typhoid fever. A diagnosis of enteric fever was made, but from the further course of the disease there was no doubt that the symptoms were attributable entirely to the tubercular infection. V. Krehl (1906) also recorded the discovery of typhoid bacilli in the blood of a case which proved at autopsy to be one of miliary tuberculosis. All such cases demand a more thorough bacteriological investigation than has hitherto been accorded them, and it would be advisable in cases of suspected miliary tuberculosis in children to examine whether the blood-serum gives a Widal reaction, and whether the typhoid bacilli can be isolated from the blood. The literature contains not a few references to the presence of agglutinins for the typhoid bacillus in the serum of tuberculous patients (Jurgens, 1907; Krencker, 1909; and others), but the most recent observations of Roth (1910) on this subject go to show that such occurrences must be very rare. The latter observer examined the sera os 100 cases of severe pulmonary tuberculosis, including five casef of the miliary form. The dilutions he employed were 1 in 50, 1 in 75, 1 in 100, and 1 in 200. Of this large series, five only gave a reaction in 1 in 50, and one in 1 in 200. This latter case was a man of forty-four years, who had never suffered from typhoid fever. Five years previously he had had an illness diagnosed as "influenza." What most of his predecessors in this field had neglected to do, Roth did: he made repeated examinations of this person's fæces, but so far he had been unable to isolate typhoid bacilli therefrom.

Several authors have reported instances which suggest that certain factors, such as trauma, pregnancy, the puerperal state, etc., may predispose to infection. Thus, Levy and Wieber

(1907) report the case of a woman who had her first child on October 1, 1906, and twelve days later had recovered from the effects of confinement. On October 21 she fell ill with typhoid fever, and the bacillus was found in her fæces. The mode of infection was doubtful, but it was found that her mother had stayed with her in the house since the birth. The mother, who was quite healthy, belonged to a village in which enteric cases had been notified in 1906. During the summer she had had an influenzal attack, which was now judged to be typhoid fever. Her stools were therefore examined, and she was found to be a carrier. Thus, the woman was apparently infected by her mother, and in Levy and Wieber's view child-bed was the predisposing cause.

Cases of enteric fever in the puerperium have not infrequently been diagnosed as puerperal fever. Levy and Wieber report in illustration of this point that two epidemics occurred in two villages near Strassburg, the one with fourteen cases, and the other with eleven cases. They were both ascribed to contact with a typhoid-sick woman in the puerperium, whose illness had not been diagnosed as such, but as puerperal fever. Two years ago I had an opportunity of examining the blood of the umbilical cord at the confinement of a typhoid carrier who had been under observation for over a year. The typhoid bacillus was recovered from the blood ; but organisms of the coli group were also present, so that some fæcal contamination of the blood, while the sample was being taken, could not definitely be excluded. The examination was undertaken in order to determine whether the general disturbance incidental to pregnancy and child-bed might induce a general typhæmia. Unfortunately, for the reasons above mentioned, the matter remains not proven. As it was, the child remained quite healthy, and the mother made a normal recovery.

Another factor has been insisted on by Conradi—viz., that strangers are most ready to contract infection when they come for the first time in contact with carriers. This proposition is a fascinating one, and certain facts observed in connection with outbreaks due to carriers may be regarded as lending it some support.

For example, we have noted that the victims of the New York cook (reported by Soper, *vide* p. 32) were frequently new servants who had only quite recently come in contact with her, while the members of the household, who had been served by her for a considerable time, escaped infection. It would be quite legitimate to suppose that the latter had gradually acquired a certain degree of immunity by the ingestion of repeated small doses of typhoid bacilli, while the new servants, not so protected, would more readily react to infection. There is, however, the further possibility that, owing to the closer contact of the servants with the carrier, the less strict cleanliness in force in the servants' hall at mealtimes and otherwise, and the use of the same privy, the dose of bacilli ingested by the servants would be liable to be greater during any given period than that ingested by the other members of the household.

Davies and Walker Hall (1908) have put forward the view that it is only at certain seasons that carriers are effective, and that for every carrier there is a particular season when infection from him or her is most likely to occur. The evidence on which this view is based is not convincing. That carriers generally are more likely to give rise to infection during the summer and autumn months has been frequently commented on, and is exactly what might be expected, in view of the greater chances that the typhoid bacillus has during this period of prolonging its extra-corporeal existence and multiplying itself before gaining entrance to a fresh host. Intermittency in the excretion of the bacillus by a carrier is certainly not always confined to the same season of the year, and may, indeed, not be observed at all even when the carrier's excreta are frequently examined over a long period. Thus, in the Brentry case, Davies and Walker Hall found that the fæces of Mrs. H. were negative during January, February and March of 1908 (three examinations). Further examinations of the fæces and urine of this carrier were made by the writer during the period June, 1908, to July, 1909 (Thomson and Ledingham, 1910). Four examinations out of six in the first three months of 1909 were found to yield positive results.

STATISTICAL DATA REGARDING THE INFECTIVITY OF CARRIERS.

This important question will receive more adequate treatment as years go on and data accumulate, and when it has become the established practice for the hygienist to co-operate with the bacteriologist in all inquiries into the origin and spread of enteric fever. Hitherto the available data have concerned only individual instances of infectivity, and, except by a few writers, no attempt has been made to employ these data for statistical purposes. Where, however, bacteriological and epidemiological inquiries have run concurrently over a fairly prolonged period, as in South-West Germany, some exceedingly striking facts have been deduced, which point to the not inconsiderable part played by carriers in the spread of enteric fever. I shall consider in the first place the recent report by Kayser (1909) on the incidence of typhoid fever in the town of Strassburg during the period summer, 1903, to spring, 1907 (nearly four years).

There were 505 cases in all (nearly 141 per annum), with a morbidity of 0·92 per 1,000 of the civil population. (In 1905 the population of Strassburg, excluding the military, was 152,271.) 6·3 per cent. of the cases were due to *B. paratyphosus* " A " or " B " (1 per cent. " A " and 5·3 per cent. " B ").

96·7 per cent. of all the cases were examined bacteriologically, and in 87 per cent. the source of infection is said to have been traced with greater or less definiteness. Thus—

13 per cent. of the cases came to the town already ill.

26·7 per cent. of the cases are stated to have contracted enteric fever by drinking raw milk, either from houses in which there were typhoid patients or from dairies in which carriers were employed.

14·6 per cent. were attributed to infection conveyed by water (use of spring or canal water), swallowing of infected water in public baths and at water sports, unclean ice, etc.

2 per cent. were attributed to food-poisoning (paratyphosus " B ").

11·9 per cent. were attributed to infection derived from contact with typhoid fever patients. Almost all these patients had been atypical or undiagnosed cases.

4·9 per cent. were professional nurses in charge of typhoid cases.

2·2 per cent. were washerwomen in contact with typhoid patients.

9·5 per cent. were attributed to infection derived from carriers (= 48 cases).

Kayser notes that some of these cases due to carrier infection were very severe. He considers that the percentage of cases attributed to infection by carriers is probably too low, and states that his figures include only those cases in which the evidence of carrier infection was absolutely conclusive. From an analysis of his cases he concluded that typhoid fever might be regarded as a disease affecting almost exclusively members of certain trades, particularly those engaged in the preparation of foodstuffs, cooks, servants, milk-sellers, and bakers. There was also some special incidence on midwives, apothecaries, and hotel staffs.

During the period indicated twenty-eight carriers were discovered in the town of Strassburg. Of these, nine were chronic carriers, eight excreted bacilli for some weeks or months, while in the remaining persons, including four children, the bacilli were found only once or twice.

Children were never found to be chronic carriers.

Of the twenty-eight carriers, eleven gave rise to typhoid cases in their neighbourhood, nine probably caused other infections, and eight gave no reason for suspicion.

To summarize, carriers accounted for at least 9·5 per cent. of the total cases of typhoid fever during the period under review.

In the cases due to milk, Kayser includes those in which the milk had been infected by typhoid carriers as well as in other ways, so that the total percentage of cases due to carrier infection (direct or indirect) is probably very much higher than 9·5.

Forster (1908) had already reported the figures relative to the typhoid cases inquired into at his institute in Strassburg during the period January, 1906, to end of June, 1907. In that time 386 cases of enteric were investigated, and 77 of these (or 20 per cent.) were attributed by him to carrier infection.

The following table shows, as regards the total number of cases of typhoid fever, the proportions in which infection was attributed to carriers and to contact with persons suffering from the fever, respectively:

	Total Cases of Typhoid Fever.	Infection by Carriers.	Percentage.	Infection by Contact with the Sick.	Percentage.
First quarter, 1906 ..	37	8	22	3	8
Second quarter, 1906 ..	62	18	29	27	44
Third quarter, 1906 ..	164	17	10	58	55
Fourth quarter, 1906 ..	57	17	30	9	16
First quarter, 1907 ..	31	8	26	7	23
Second quarter, 1907 ..	35	9	26	13	37
Total	386	77	—	117	—

The percentage of cases due to carriers rose as high as 30 in one quarter, and the average for the eighteen months under review worked out at 20.

In Forster's view, this percentage is probably too low, as it is possible that many of the small water- or milk-spread infections may have been directly due to some carrier focus acting only for a very short period.

I come now to consider the statistics for the whole campaign during the four years ending December 31, 1907. The figures for 1904, 1905, and 1906, are given by Frosch (1907). During that time, as I have already observed, there were 6,708 typhoid fever cases, of whom 310 became carriers (144 transitory, 166 chronic). Of these 6,708 infections, 215 were in all probability attributable to carriers, and 61 were attributable to carriers with less probability—*i.e.*, 276 infections, or 4·11 per cent. of the total number, were ascribed to carriers. The figures for the year 1906 are, however, the only ones available for determining the relative shares of carrier and other agencies in the propagation of typhoid fever.

In 1906 there were 2,080 cases of enteric fever, and in 978 the source was explained (*i.e.*, 47·7 per cent.). Of these 978 cases, 642 were attributed to contact with infectious persons (= 28·5 per cent. of the total cases, or 65·14 per cent. of the explained cases). Included in the explained cases are 104 in which it was an open question whether direct or indirect contact was involved. Adding these 104 to the cases definitely attributed to contact, we get a total of 746 (= 36·02 per cent. of the total cases, or 76·2 per cent. of the explained cases).

232 infections were attributed to drinking contaminated water, contaminated milk, foodstuffs, etc. (= 11·15 per cent. of total, or 23·7 per cent. of explained cases).

1·76 per cent. of the total were imported cases.

Of the 642 contact cases, 49 were due to contact with carriers (= 2·35 per cent. of total cases, or 5·01 per cent. of the explained cases).

Thus, about one-fourteenth of all contact infections were due to carriers, while the remaining thirteen-fourteenths were due to ordinary cases of typhoid fever.

Before they were discovered, 310 carriers caused 228 infections (= 3·41 per cent. of all cases), while after their discovery and the enforcement of requisite precautions only 48 infections arose from them—*i.e.*, known carriers were responsible for 0·7 per cent. of all infections.

Klinger (1909), in a more recent report, gives the figures up to the end of 1907. The carriers had now mounted to 431, and the total number of infections attributed to them was 351—viz., 51 due to transitory carriers, and 300 due to chronic carriers.

These numbers appear small in comparison with the total number of typhoid cases, and, if cursorily considered, might be held to imply that the danger from the carrier infection was a relatively small one ; but it has to be remembered that, though a carrier may infect directly or indirectly one single person, the latter may propagate the infection widely. In fact, endemic prevalences of typhoid fever on a fairly large scale have in the last resort been found to be traceable to a carrier who was responsible only for the first link in the chain.

In the foregoing statistics this view of the matter is not taken into consideration. The carrier is held responsible only for the first link.

For the attainment of complete statistics on the sources of typhoid infection, it is necessary that the epidemiologist should not be content to stop his inquiries at the point where he has been able to demonstrate a case of typhoid fever as the immediate source of infection.

These considerations have been insisted upon by Schumacher (1909) in his report on endemic typhoid fever at Cröv, in the district of Trier. He comments on the fact that, according to Frosch's collected figures, only 47·4 per cent. of the total cases were explained, and contends that the percentage of cases due to carriers would probably have been found to be much higher had the investigations of the epidemiologist and the bacteriologist been prosecuted with greater insistence. The bacteriological work carried out in connection with endemic typhoid fever at Cröv, a small typhoid-ridden village, containing about 1,750 inhabitants, was limited only by the reluctance exhibited by a few families to provide material for examination, and even this appears to have been successfully overcome. It is impossible here to detail the whole course of the investigations. The original paper must be consulted, and will repay careful study, as it is fully provided with charts of the village showing the houses in which cases of typhoid fever occurred in the different years, and those houses in which carriers were resident. I must confine myself here to the actual statistics.

During the period 1903 to 1908, 45 cases in all occurred. Of this total, only 24—*i.e.*, 51·1 per cent.—had been explained by previous inquiries. As the result of the extensive bacteriological work carried out by Schumacher in the village, practically all the 45 cases received adequate explanation. The following are the figures relating to the different modes of infection :

Imported cases	6 = 13·4 per cent.	(previous inquiry, 4).
Contact with typhoid cases ..	20 = 44·4 ,,	(,, ,, 20).
Cases in which it was doubtful whether the infection arose from carriers or typhoid cases ..	7 = 15·6 ,,	(,, ,, 0).
Contact with carriers	12 = 26·6 ,,	(,, ,, 0).

Schumacher says that "the discovery of the chronic carrier gave the key to the explanation of endemic typhoid in Cröv." The large percentage of 26·6 per cent. is in striking contrast to that of Frosch (quoted above), and Schumacher suggests that the explanation of the discrepancy is to be found in the following considerations :

1. The proportion of explained cases depends on the time that can be spent on the inquiry, on the persistence with which the bacteriological work can be carried out, and, finally, on the willingness of the people concerned to supply samples for examination. In Cröv these conditions were fully satisfied, whereas the collected data of Frosch were certainly not based on work of such uniform completeness.

2. It frequently happens that the responsible carrier cannot be detected till some considerable period has elapsed, and when, possibly, the statistics have been already made up.

3. The statistics only take account of the fact that the first link in a chain of cases was attributable to a particular carrier, whereas the whole chain of cases should really be put to the charge of the carrier, if the importance of the latter is to be rated at its true value.

If in the figures for Cröv this latter consideration was taken into account, the number of cases directly due to carriers (viz., 12) would have received an accession of 8 indirect cases, giving a total of 20—*i.e.*, 44·4 per cent. These additional 8 cases were due to infection from typhoid cases in chains started by carriers.

I close this section with the data collected by G. Mayer (1910) regarding endemic typhoid fever in the Bavarian Pfalz. The bacteriological work was carried out, apparently, in the most complete manner, and to Mayer we are indebted for many important and elemental facts with regard to intermittency and the occurrence of typhoid bacilli in the excreta during the incubation period. In previous sections many of these data have been referred to. Here I give Mayer's figures relative to the infections caused by carriers :

	Number of Infective Carriers.	Cases of Typhoid directly due to these.	Site of Infection.					
			In Dwellings.	Business.	Bureau.	Social Intercourse.	School.	Shops dealing in Foodstuffs.
1904 ..	19	63	17	1	2	3	5	4
1905 ..	12	33	12	—	2	—	2	2
1906 ..	25	43	19	—	—	2	3	3
1907 ..	16	21	14	—	—	—	1	1
Total	72	160	62	1	4	5	11	10

During this period there was a total of 495 endemic cases, for 160, or 32·3 per cent., of which carriers were held responsible. As will be seen, this figure corresponds fairly closely with that obtained by Schumacher.

With regard to the conditions under which the carriers were infective, the table shows that the great majority of the infections due to carriers arose in the domestic circle, while the school and food shops (bakery, dairy, inns, etc.) constituted a good second. In Mayer's view, the unclean hand of the carrier is in most cases the agent which transfers infection to the new host.*

IMMUNITY QUESTIONS IN CARRIERS.

In previous sections incidental references have been made to the antibodies demonstrable in the serum of the typhoid carrier. For diagnostic purposes, at least, the agglutination test has hitherto proved of most service, and I have already discussed the value of this reaction and its limitations (*vide* p. 102).

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* Brückner has recently (August, 1912) analyzed the epidemiological and bacteriological data with regard to typhoid outbreaks occurring in the Saarbrücken area during 1911. There were in all twenty-eight epidemic chains, each containing not less than six, and sometimes as many as sixty-nine cases. These chains of cases were in fourteen instances traceable to typhoid-sick persons, and in the remaining fourteen to carriers, several of whom were previously declared carriers. The vehicle by which infection was conveyed from the carrier to the new hosts was, in a surprising number of cases, either milk or foodstuffs such as vegetables, fruit, etc.

Here I propose to enter a little more fully into the immunity side of the carrier question in so far as the recorded facts warrant.

In the first place, with regard to the agglutinins, about two-thirds to three-quarters of all chronic carriers give a well-marked Widal reaction (titre of 1 in 100, or at least 1 in 50). Some, indeed, have been found to exhibit a very high agglutinin content (up to 1 in 2,000 or higher), but such high titres are generally associated with an intercurrent acute infection or auto-infection, such as cholecystitis.

Owing in great measure to the reluctance of healthy carriers to furnish specimens of serum, and the insufficient facilities for work of this nature in institutions where carriers are isolated, our knowledge of the variations in the agglutinin content of carrier sera over a long period is very deficient. An investigation of this matter might yield results of great value.

With regard to the transitory carrier who has never had any obvious symptoms of typhoid fever, or who has so far not developed symptoms, definite statement as to the course of the agglutinins cannot yet be made. We know that typhoid bacilli may be excreted in the fæces, and may even be circulating in the blood-stream, for some considerable time before the agglutinins make their appearance in the serum. This fact may explain the recorded absence of a Widal reaction in a certain proportion of transitory carriers. On the other hand, a development of agglutinins has been observed to occur in the so-called "symptomless" cases of typhoid fever (Lentz, Scheller, already cited), who are found to discharge bacilli for very short periods. It is important to remember these points in those cases in which the physician has a positive reaction reported to him, which, however, does not appear to be associated with any definite symptoms of the disease. Such cases undoubtedly occur, and may give rise to considerable scepticism as to the value of the Widal test. For the satisfaction of the physician and the bacteriologist, an attempt should always be made to examine the excreta, in view of the possibility of such cases being really temporary carriers.

I have already discussed certain other limitations of the Widal test in carriers, particularly its not uncommon occurrence in cases of miliary tuberculosis which do not exhibit typhoidal lesions at autopsy. In this type of case the excreta should always be bacteriologically examined, especially in children, in whom notoriously the course of typhoid may be atypical. It would take too much space to enter into the question of positive Widal results either in typhoid carriers who also harbour organisms of the Gaertner-paratyphoid group or in persons infected with members of this group only. The presence of a co-agglutinin for *B. typhosus* in the serum of food-poisoning cases is now well established, though no satisfactory explanation has hitherto been given.

One other point relating to the agglutinins in carrier sera has to be observed. The serum of the carrier may agglutinate with ease the bacilli of a laboratory strain, but may have little or no influence on the homologous strain. It must be noted, however, that the reaction with the homologous strain may occur late, the velocity of reaction being much slower than with the stock strain.

Ledingham (1908) recorded the results with two carrier sera tested, both with the stock strain and with the homologous and other carrier strains. One of them gave a marked reaction with the laboratory strain only, but with the homologous strain and another carrier strain there was merely a trace of agglutination after nine hours. On the other hand, another carrier serum was able to agglutinate with equal ease all three strains. Kennedy (1910) records similar results.

In those carriers in which no agglutination of the homologous strain takes place, one cannot assume that the serum contains no suitable receptors of any kind for this strain, as we know that the serum may still possess a high opsonic or tropic content towards the homologous bacillus. Further, as we shall see, there may be no agglutinins in the serum either for stock or homologous strains, and yet complement-deviating bodies may be demonstrable.

The influence of vaccination (with typhoid vaccines) on the agglutinin content of carrier sera varies greatly. In one case (Thomson and Ledingham, 1910) the titre rose from less than 1 in 20 to 1 in 800 towards the stock strain, and to 1 in 400 towards the homologous strain. Recently, however, I have had a case in which the agglutinins remained stationary even after a course of vaccination with the patient's own strain. Kennedy (1910) has also published charts showing in two cases either no change or only a very insignificant rise in the agglutinins, and in one case a stationary titre followed by a marked rise to 1 in 300 after the use of a specific vaccine.

Walker Hall and Roberts (*loc. cit.*) obtained agglutination with the serum of their female urinary carrier, in a dilution of 1 in 1,860, during the periods of active excretion of the bacillus. When, however, the vaccine was being given, and the bacilli disappeared temporarily from the urine (see p. 100), the agglutinin titre gradually fell till the dose of 1,000,000,000 was reached. A slight rise to 1 in 230 or 1 in 460 then took place.

Bactericidal Substances.

Observations on the bactericidal power of the serum of carriers are few, and these go to show that little or no variation from the normal standard occurs.

On two occasions (Ledingham, 1908) I have tested the sera of three carriers against the homologous and other strains (*in vitro* tests). The sera were inactivated and complemented with fresh guinea-pig serum. Some increase in the bactericidal power of the serum was found over that of the control serum, but the differences appeared to depend largely on variations in the resistance of the strains employed.

A sufficient quantity of serum for experiments of this nature is not readily available. Niepratschk (*vide* p. 57) tested by the Pfeiffer method the bactericidal power of the serum of his urinary carrier. The virulence of the carrier strain was raised by passage through the guinea-pig from one-quarter of a whole agar culture to one-quarter of a loop (= minimal lethal dose for guinea-pig of 250 grammes by intraperitoneal inoculation). With this strain and the carrier serum he made the following experiment:

Guinea-Pig.		Result.
A ..	¼ loop + 1 c.c. of 1 in 200 dilution of serum	Death after 24 hours.
B ..	¼ ,, +1 ,, 1 ,, 100 ,, ,,	,, 24 ,,
C ..	¼ ,, +1 ,, 1 ,, 50 ,, ,,	,, 24 ,,
D ..	¼ ,, +1 ,, 1 ,, 25 ,, ,,	Lived.
E ..	¼ ,, +1 ,, 1 ,, 10 ,, ,,	,,
F ..	¼ ,, without serum.	Death.

The bactericidal titre therefore lay between 0·02 and 0·04, and was thus very low. During the vaccination of a typhoid carrier, Meader (1910) obtained a decided rise in the bactericidal titre of the serum.

Opsonic Substances.

Ledingham (1908) found a very marked increase in the opsonic content of carrier sera towards homologous strains, indices of 4 to 9 being obtained. Further, this opsonic substance disappeared almost completely on inactivation of the serum, but was readily restored on complementing with fresh normal serum, which of itself had little opsonic value. An opsonic amboceptor was thus demonstrated in carrier sera.

Gaehtgens (1909) examined sixteen carrier sera, and found in all except one (an intermittent case) a marked increase in the opsonic content. He also tested the sera of a number of persons who had had enteric at varying periods previously, but who were not carriers. An increase of opsonic power could be demonstrated only in those whose attack dated three or four months back.

Kennedy (1910) has also reported a considerable increase in the opsonic content of carrier sera. During vaccination a further steady rise takes place, which may not be accompanied by any definite increase in the agglutinin content.

Hamilton (1910) has also found abnormal opsonic indices in typhoid carriers, and recommends the opsonic tests in the preliminary search for carriers.

Complement Fixation Experiments with the Serum of Carriers.

Schöne (1908) investigated this question in three carriers, and in the serum of two of these he was able to demonstrate quite definitely the presence of complement-fixing bodies. Henderson-Smith (personal communication) has also been successful in demonstrating these substances in the sera of two untreated typhoid carriers, both of whom gave completely negative Widal reactions.

In concluding this section one feels compelled to admit that specific antibodies for the typhoid bacillus do pass over into the general blood-stream in typhoid carriers, although the vegetative foci may be considered to be in great measure shut off from, or even, as some would suggest, entirely outside, the influence of the general circulation. The "local immunity" theory of Wassermann and Citron (1905) can only, therefore, afford a partial explanation of the prolonged vegetation of the typhoid bacillus in the gall-bladder and biliary tracts. Much work yet remains to be done on the immunity aspect of the carrier question.

VARIOUS MEASURES EITHER EMPLOYED OR SUGGESTED TO DIMINISH THE SPREAD OF INFECTION BY CARRIERS.

In this concluding section I propose to discuss briefly the various precautions which have been adopted or recommended by sanitary authorities and others in order to reduce as far as possible the risk of infection from carriers. Pending the discovery of some efficient mode of therapy, all attempts to cope with this danger by sanitary measures are worthy of the most serious consideration at the present time. Obviously, the first step is the adoption of some form of routine bacteriological examination during convalescence, and in previous sections I have sufficiently alluded to the practice in vogue at the typhoid stations in Germany and elsewhere, and to the drawbacks from which practically every stereotyped routine must suffer, owing to intermittency, imperfection of bacteriological method, or both. Still, there is no doubt that much good can be accomplished by the early recognition of carriers, and experience has shown that the longer the duration of bacteriological supervision, the less is the risk of overlooking the intermittent carrier. Monthly examinations of the excreta of all convalescents for a period of one year would probably suffice.

At the instigation of the Local Government Board, with the co-operation of the Metropolitan Asylums Board, Dr. Theodore Thomson and the writer undertook the bacteriological supervision of typhoid fever convalescents during a period of two years. A report dealing with the results obtained and the practicability of the scheme will appear in the course of the present year (1912).

Otto Mayer (1909) has suggested in a recent paper the foundation of convalescent homes for recovered typhoid cases. In such homes the convalescent who is still excreting the specific bacilli on discharge from hospital would be retained. By suitable treatment, dietetic and otherwise, by gymnastic exercises, etc., efforts would be made to encourage the physiological excretion of typhoid bacilli until possibly complete cessation resulted. Whereas many convalescents are compelled to resume their active duties at a far too early stage, when consequently the natural recuperative powers of the organism do not get an opportunity of throwing off an infection that is tending to become indolent, in the convalescent home every opportunity would be afforded to the bactericidal and antitoxic powers of the organism of exercising their full effect. Full and accurate statistics would be kept regarding the duration and severity of the disease, the diet employed in convalescence and in the home, the muscular power of the patient, and the bacteriological results. Such statistics would later prove of great value in deciding the influence exerted by the treatment during convalescence on the carrier output.

There is no doubt that such institutions would prove of service in many ways. The patients that would ultimately have to be discharged in a potentially infective condition would be accurately instructed as to the precautions they should take on their return to civil life. This of itself would be a great gain, as the difficulty of impressing on unintelligent carriers the necessity of taking strict precautions as to disinfection has proved a serious stumbling-block.

In institutions such as lunatic asylums, the problem of dealing with chronic carriers who are also chronic lunatics is solved by the simple and successful expedient of isolation. This measure, however, may prove an expensive one, especially in the case of small institutions, as it may involve the upkeep of an isolation block, with special attendants for a period coincident with the life of the patient.

Grimme (1908) has stated that prolonged isolation is unfavourable to the patient, as little or no intercourse is possible, and the patients themselves do not see the necessity for the detention. This may certainly be true in some cases, but so far as the asylum cases that I have had under bacteriological supervision for over four years are concerned, I am informed that isolation has had no prejudicial effect. It may be otherwise with acute lunatics who are carriers.

Every new patient, on entrance into the asylum, should be examined bacteriologically.

These lunatic carriers in asylums constitute, undoubtedly, the best material for the investigation of the carrier status, for the simple reason that it is always available. Prolonged trials of various therapeutic agents can be readily carried out, and intensive bacteriological studies can be undertaken, provided the necessary facilities for such work are to hand. The latter condition is, however, rarely satisfied, and it would seem to me a question worthy of consideration, whether all such carriers could not be drafted to some central institute (perhaps in connection with a large fever hospital), where a competent bacteriologist, acting under an advisory committee, might undertake a special study of the many problems presented by the carrier state. In such an institute provision might also be made for the reception of sane carriers who may offer themselves for study.

In the army, measures have already been taken for dealing with known carriers. If after a course of therapeutic treatment the carrier condition persists, the soldier is discharged from service, with or without a pension, according as he agrees or not to the notification on his discharge-sheet that he is a chronic typhoid carrier. Drastic steps have also been taken to prevent the employment of regimental cooks who may happen to be carriers.

In the civil population, the problem of dealing effectively with carriers revealed in the course of inquiries into occurrences of enteric fever presents difficulties which only the future can solve. At present much good is being done in South-West Germany and elsewhere by retaining all carriers under bacteriological supervision, by giving suitable instruction with regard to disinfection of their excreta and their persons (particularly their hands), and by oral and verbal advice as to the occupations they should avoid. A useful series of Standing Orders employed in the Pfalz stations accompanies a paper by G. Mayer (1910). Of one of these, dealing with typhoid carriers and convalescents, I give a translation; it has been in force since 1904:

1. Typhoid carriers and clinically cured cases are retained under bacteriological supervision until a bacteriological cure results.

2. So long as they discharge bacilli, the official disinfectors carry out or supervise the continual disinfection of privies used by them (with milk of lime).

3. In the case of school-children, workers in factories and such-like, teachers, officials in State and private bureaus, these may carry on their respective duties provided that the schools, factories, etc., are supplied with suitable wash-basins and soap. On commencing duty and on every occasion when the privy or urinal is visited the hands must be cleansed.

4. In dwellings, the disinfection of privies and urinals is systematically carried out by the official disinfectors (with milk of lime).

5. Typhoid carriers are to be restrained from the preparation and sale of foodstuffs.

Instructive pamphlets are also issued to every newly-discovered carrier. The following is a free translation of that issued to carriers by the typhoid station at Strassburg (quoted from Gaehtgens, 1910).

Instructions for Typhoid Carriers.

1. Typhoid fever in its severest form runs the course of a nervous fever. In its slighter forms it is accompanied by diarrhœal symptoms, but frequently the symptoms of the disease are scarcely noticeable.

It is caused by a specific bacillus—the typhoid bacillus.

2. The typhoid patient harbours the typhoid bacilli in his body, and discharges them during the disease with the stools and urine.

3. Some persons may continue to discharge typhoid bacilli in the fæces for months or years after convalescence, or even although there has been no obvious primary attack. These persons are called "typhoid carriers."

4. Typhoid carriers suffer as a rule from gall-bladder troubles, which give rise to transitory colic, jaundice, and gall-stones, but frequently these symptoms are not present.

5. Carriers may infect other persons with typhoid fever just as typhoid patients do.

6. Infection occurs most frequently by the hands, which are readily contaminated with typhoid bacilli during defæcation and urination. Infection may also be spread by soiled body and bed linen.

7. The bacilli get transferred from the unclean hands to other persons either by direct contact or by indirect contact—*e.g.*, with foodstuffs and various objects used by other persons.

8. It is possible for typhoid carriers to reinfect themselves. In such cases one may expect an aggravation of the already existing gall-bladder troubles.

9. Carriers may avoid infecting other persons or themselves by the following precautions:

(*a*) The carrier must always exercise the greatest cleanliness.

(*b*) Hands should be thoroughly washed on getting up in the morning, before every meal, and before touching food or drink (especially milk).

(*c*) The carrier must, after using the water-closet, cleanse the hands thoroughly with soap and water or with a disinfectant.

There should always be a sufficient quantity of closet-paper in the water-closet.

(*d*) The carrier must have his own towel, which no one else may use.

(*e*) The carrier's dirty body and bed linen should, before washing, be dipped in cresol-water (2 tablespoonfuls of cresol-soap solution to 1 litre of water).

(*f*) The carrier should as far as possible avoid taking part in the actual preparation of food or in its sale.

10. It is to the carrier's own interest that he or she should send, about once a month, a specimen of the stools and of the urine to the Bacteriological Institute at Strassburg, in order that it may be determined whether the excreta still contain typhoid bacilli. The examination is done gratis. Suitable vessels for the reception of excreta are sent post free from the Institute.

11. The Institute is very pleased to give advice regarding the disinfectant to be used by carriers.

12. The precautions advised above are absolutely indispensable, and it is morally incumbent on carriers to adhere to them in order to avoid infecting other people.

There is no doubt that much good has already been accomplished by instructing typhoid carriers in proper methods of disinfection, and it is on the disinfection of the hands that chief stress must be laid. Gaehtgens (1910) has performed an interesting series of experiments designed to determine the most efficient, and at the same time the least irksome, method of cleansing the hands of typhoid carriers. He smeared the hands and fingers with fæces containing typhoid bacilli, and determined the relative disinfectant values of mechanical washing, with and without disinfectants, and followed or not followed by thorough drying. He found that washing with soap and water alone, without subsequent drying of the hands, caused a marked fall in the number of *B. coli* and *B. typhosus*, especially of the former. If, however, the hands were dried thoroughly after removal of the soap in running water, subsequent cultivation frequently showed a complete disappearance of *B. coli* and *B. typhosus*.

For those carriers, therefore, who are not specially engaged in handling foodstuffs, the mechanical cleansing of the hands with soap and water and subsequent drying affords a tolerably complete protection. For those carriers, on the other hand, whose occupation entails the handling of such material, it is advisable to employ an antiseptic after the ordinary washing and drying process, in order to insure complete removal of any typhoid germs still clinging to the hands. For this purpose Gaehtgens found that the most satisfactory disinfectant was alcohol, either in the form of eau-de-Cologne or spirits of wine.

The question of legislative measures for the control of declared typhoid carriers may have to be faced in the future, and more particularly of those carriers whose occupation in the handling and sale of foodstuffs renders them peculiarly liable to transmit infection to others.

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CHAPTER III

PARATYPHOID FEVER, AND THE INFECTIONS CAUSED BY ORGANISMS OF THE GAERTNER-PARATYPHOID GROUP

I. INTRODUCTORY.

THE discussion of paratyphoid fever and the etiological rôle of carriers in connection therewith is at the present time an undoubtedly difficult task, by reason of lack of settled opinion, partly among bacteriologists and partly among clinicians. In this country paratyphoid fever does not appear to have received from the clinician the attention which its importance deserves, and we have little doubt that numerous genuine cases of this disease, running a typhoid-like course, are returned as enteric fever owing to a reluctance on the part of the clinician to recognize the fact that two infectious diseases, presenting slight but definite differences in symptomatology and course, may have entirely different etiologies. It is with the bacteriologist that the ultimate diagnosis must rest, and he, either through lack of stimulus from the clinical side or of opportunity of independent bedside observation, is often precluded from making adequate bacteriological investigation. Boycott (1906) calculated that about 3 per cent. of cases of notified enteric fever in this country are really paratyphoid fever, and Savage (1908-09) comes to a similar conclusion; but it is probable that the percentage is considerably higher. It is generally agreed, among those who have directed special attention to the subject, that paratyphoid fever presents certain notable peculiarities in its symptoms and course which mark it off fairly definitely from the typical case of enteric fever. To detail these features would be out of place here. Suffice it to state that in paratyphoid fever the onset is often sudden and alarming, with high fever, but that the general course of the infection is milder and of shorter duration. In his Milroy Lectures, 1912, Dr. Bainbridge gives an account of the chief clinical features of paratyphoid fever, and to this account the reader may be referred. Of the more recent clinical accounts of paratyphoid fever in German, that of Rolly (1911) may be read with advantage. For a description of the clinical features of paratyphoid A fever as it is met with in India, recent reports by army medical officers should be consulted (Grattan and Wood, 1911).

As in typhoid fever, however, the symptoms may vary greatly in severity, and it has also to be remembered, as was pointed out originally by Schotmüller, that infection by the paratyphoid bacillus may take the form of an acute gastro-enteritis, thus simulating in clinical aspect what is rather loosely termed "food-poisoning."

The paratyphoid bacilli belong to what is known as the "Gaertner-paratyphoid group of organisms," two of which—viz., *B. paratyphosus B* and *B. paratyphosus A*—are associated mainly with certain forms of continued fever of typhoid-like type (paratyphoid fever), and also occasionally with gastro-enteritis; while the other two—viz., *B. enteritidis Gaertner* and *B. suipestifer* (or *B. aertryck*)—are associated with outbreaks of food-poisoning. Of this group, *B. enteritidis* was isolated in 1888 by Gaertner from meat which was regarded as the cause of a food-poisoning outbreak, and also from the organs of a patient who had succumbed. Ten years later Durham (1898) and De Nobele (1898) recovered from cases of food-poisoning and from suspected food an organism possessing the cultural characters of *B. enteritidis*, but distinguishable from it by agglutination tests. This organism was called *B. aertryck*, from the name of the village where the outbreak described by De Nobele occurred. The *B. suipestifer*, which research has shown to be identical with *B. aertryck*, is an organism which occurs in the alimentary canal of healthy pigs, and more especially in the organs of pigs which have succumbed to swine fever, of which it was considered to be the specific cause until the experiments of Dorset and Bolton and McBryde (1905) proved that a filter-passing virus was the essential causative agent.

The remaining two members of the group—*B. paratyphosus B* and *B. paratyphosus A*—were isolated by Schottmüller (1900-01) from the blood of patients whose clinical symptoms resembled those of enteric fever. Similar organisms, however, had been isolated some years prior to Schottmüller's communication, by Gwyn (1898), Achard and Bensaude (1896), etc. The name "paratyphoid" we owe to the two French observers. In this section we shall be concerned mainly with *B. paratyphosus B* and its relation to paratyphoid fever. Infections by *B. paratyphosus A* have been extremely rare in Europe, but recent work by army medical officers in India has shown that in that country it practically takes the place of *B. paratyphosus B*. In view of its importance as the cause of irregular pyrexias among British troops in India, it will be considered separately (*vide* p. 156).

II. CULTURAL CHARACTERS, AND METHODS OF DIFFERENTIATING THESE FOUR ORGANISMS.

All observers are agreed that culturally and biochemically three of the four members—viz., *B. suipestifer*, *B. enteritidis Gaertner*, and *B. paratyphosus B*—are indistinguishable. They are all motile, Gram-negative bacilli, having no action on lactose. In certain other carbohydrate fluid media—glucose, mannite, dulcite, lævulose, galactose, maltose, and arabinose—they produce acid with gas formation, but no change is observed in media containing lactose, saccharose, raffinose, salicin, and inulin. Occasionally strains of *B. suipestifer* are found which render acid the appropriate media, but have lost the power of gas production (Bainbridge, 1909; Bock, 1906). Litmus milk becomes alkaline after an initial acidity, and no indol is produced in peptone broth. *B. paratyphosus A* differs from the others only in its action on litmus milk, which remains acid (as in the case of *B. typhosus*).

By agglutination methods *B. enteritidis Gaertner* and B. *paratyphosus A* can be easily separated off, while it is possible by absorption methods only to separate *B. suipestifer* from *B. paratyphosus B*. Many German writers who have not employed absorption methods maintain the view that *B. suipestifer* and *B. paratyphosus B* are indistinguishable, and hence has arisen the difficulty we have had in appraising at their true value many of the German observations based on this view. Boycott (1906), Bainbridge (1909), and Bainbridge and O'Brien (1911), in this country have, as we think, very clearly shown the possibility of differentiating these organisms by absorption methods, and the complement fixation experiments of H. R. Dean (1911) have gone far to support their conclusions.

METHOD OF ISOLATION.

The various media employed in the isolation of *B. typhosus* from excreta (see p. 106) are equally suitable in the case of the Gaertner-paratyphoid group. The writer has used mainly MacConkey's bile-salt-lactose-neutral-red-agar, but some observers recommend strongly the employment of malachite-green media for the isolation of members of this group. The excreta may either be plated directly on the malachite-green agar plates or inoculated into malachite-green broth as a preliminary enriching medium. In the latter case the malachite-green broth tubes are incubated overnight at 37° C., and finally plated on Conradi-Drigalski or Endo plates (method recommended by McWeeney, 1911). The colourless colonies which develop on the MacConkey plates are picked off into tubes of dulcite-peptone-water. If acid production with formation of gas occurs (as shown by the Durham tube) in any of the tubes, subplants should be made from the tubes in question into lactose, mannite, and cane-sugar. There is an advantage in retesting the strain on lactose, as one is occasionally deceived by assuming that colourless colonies on a MacConkey plate that has not been incubated sufficiently long, are non-lactose fermenters. For the motility test young broth cultures should be used. Indol should be tested for by the paradimethylamidobenzaldehyde method. Tubes of litmus milk should also be inoculated. As it is only by serological methods that *B. enteritidis Gaertner*, *B. suipestifer*, and *B. paratyphosus B*, can be differentiated from each other, it is absolutely essential to have a supply of potent specific antisera prepared by immunization with standard strains of these organisms. By agglutination tests only, it is easy to determine whether one is dealing with *B. enteritidis Gaertner*. A specific *paratyphosus A* antiserum is also absolutely essential for agglutination purposes, if the suspected organism conforms culturally and biochemically with *B. paratyphosus A*. In order to determine whether a suspected organism, which we have found to be agglutinated, probably equally well by both *paratyphosus B* and *suipestifer* antisera, is either the one or the other, it is necessary to perform absorption tests. It is impossible to discuss here the technical details of the method. They will be found in a paper by Bainbridge and O'Brien (1911), who supply numerous illustrative examples. These authors recommend the use of two absorbed sera—viz., (1) a specific *paratyphosus B* antiserum which has been absorbed with a standard strain of *B. suipestifer*; (2) a specific *B. suipestifer* antiserum which has been absorbed with a standard strain of *B. paratyphosus B*. The absorbed sera are then finally tested both against the unknown strain and the standard strains by the macroscopic agglutination method. This method is particularly useful if a large number of unknown strains have to be tested at the same time.

III. THE DISTRIBUTION OF THE GAERTNER-PARATYPHOID GROUP OF BACILLI IN MAN AND OTHER ANIMALS.

In the previous section we have dealt with the various criteria employed for the differentiation of the four important members of this group, and we have put forward the evidence which has led Boycott and Bainbridge to the conclusion that *B. paratyphosus B* is distinguishable from *B. aertryck*, and that the latter is identical with *B. suipestifer*. Having had an opportunity of observing the striking differences between *B. paratyphosus B* and *B. suipestifer*, which can be elicited by carefully-performed absorption tests, and having regard to the important bearing of such findings on the epidemiology of the group generally (see Bainbridge, 1912, Milroy Lectures), we are now in a position to discuss the most recent contributions to our knowledge of the distribution of these organisms in Nature. Without some discussion of the distribution of this group, it would be impossible to form a correct appreciation of the facts relating to the paratyphoid carrier, and at the present time a frank discussion of this subject is all the more necessary, in view of the fact that some bacteriologists of repute have—as we think, on entirely insufficient grounds—made out a claim for the ubiquity of the paratyphoid bacillus. The failure of many of these bacteriologists to establish the identity of the paratyphoid-like organisms isolated by them, by rigorous differential tests, is calculated to give the reader who is not specially versed in this subject an entirely false impression of the state of affairs. We are convinced that too much attention is still paid by some workers to the appearance and colour of colonies on Conradi-Drigalski plates and similar differential solid media, and too little to the other biochemical reactions, including more particularly fermentation tests and indol production. On the strength of cultural and biochemical tests alone an organism may qualify for admission to the Gaertner-paratyphoid group, further identification depending on serological analysis. The use of dulcite must at the present time be regarded as essential. In fact, one frequently notes the employment of carbohydrate media which, in the absence of dulcite, have no differential value whatever, so far as this group is concerned. The possibility, of course, is not precluded that in future some other carbohydrate medium may be found to give an additional means of differentiation, and in this connection one might refer to the recent observations of Reiner Müller (1911), who showed that on raffinose plates strains of *B. paratyphosus B* form colonies with secondary papillæ (*Knöpfe*), while strains of *B. suipestifer* do not. This method of differentiation has been employed by Penfold (1912), who has examined large numbers of "paratyphoid" strains from various sources. The strains which developed papillæ were all derived from cases of paratyphoid fever or carriers, while those which did not (but which their discoverers were unable to distinguish from paratyphoid) had their source in foodstuffs, wholesome or otherwise, and were, from Bainbridge's absorption results, in reality *B. suipestifer*. The differentiation thus obtained by raffinose lends marked support to the contention that *B. paratyphosus B* is distinct from *B. suipestifer*.

Distribution of B. Paratyphosus B and B. Suipestifer apart from Cases of Paratyphoid Fever.

It is necessary in the meantime to consider these two organisms together, as in Germany no distinction, as a rule, is drawn between them, and, irrespective of their source, they are generally reported as paratyphoid bacilli.

Uhlenhuth, Hübener, Xylander, and Bohtz (1908), in the course of their experiments on the etiology of swine fever, in which they confirmed the results of Dorset, Bolton, and McBryde (1905), that a filter-passing and not the hog cholera organism (*B. suipestifer*), so frequently present in such cases, was the essential cause of the disease, examined the fæces of a large number of healthy swine. From 8·4 per cent. of the samples they obtained *B. paratyphosus B* or *B. suipestifer*. Seiffert (1909) also obtained this organism from 3·5 per cent. of healthy swine.

Schmidt (1911) examined 700 swine, and from the fæces of 4 per cent. paratyphoid-like organisms were isolated. Culturally they agreed with *B. paratyphosus B*, but they were agglutinated only in low dilution by *paratyphosus B* serum and hog cholera serum. The fact that two-thirds of these strains formed indol led him finally to conclude that the strains isolated were not genuine paratyphoid bacilli. Indol-forming organisms with Gaertner-like characters were found many years ago by Morgan (1906-07) in human and other fæces, and quite recently Horn and Huber (1911) have found them in horse and cow fæces, and also in flies. The latter observers rightly consider that their results lend no support to the "ubiquity" theory. It may be noted here, however, that a genuine *B. paratyphosus B* was on one occasion isolated by Nicoll (1911) from a house-fly.

Savage (1908-09) examined the excreta of healthy cattle and horses, and failed to find *B. suipestifer*; and a similarly negative result was got by Bainbridge (1911) in the course of an examination of fifty healthy pigs in this country.

In a guinea-pig epizoötic, which was most probably due to a filter-passing virus, Petrie and O'Brien (1910) isolated from many of the fatal cases an organism which they definitely identified as *B. suipestifer*. This organism can undoubtedly produce lesions in the organs of guinea-pigs simulating those caused by *B. pseudo-tuberculosis rodentium*. Bofinger (1911), Dieterlen (1909), and others, have also recovered what they consider to be *B. paratyphosus B* from yellow nodules in the liver and spleen of guinea-pigs.

Also in the infectious enteritis of canaries "paratyphoid" bacilli have been recorded. In a recent paper by Adam and Meder (1912) an organism indistinguishable from *B. para-*

typhosus B was recovered, but no absorption experiments were performed with the view of differentiating the organism from *B. suipestifer.*

Examination of Foodstuffs.

Hübener (1908) isolated organisms indistinguishable from *B. paratyphosus B* from 6 out of 100 samples of sausages drawn from various sources. None of them had given rise to food-poisoning. The bacilli were recovered from the interior of the sausages, and were only in scanty numbers. Rommeler (1909) also found "paratyphoid" bacilli in 8 out of 50 samples of sausage, and in 5 out of 8 samples of raw minced meat.

Mühlens, Dahm, and Fürst (1909), examined 57 different kinds of meat by direct plating, and found them all negative. By feeding experiments with these apparently sound foodstuffs, they recovered from the mice which succumbed organisms corresponding either with *B. enteritidis Gaertner* or with *B. paratyphosus B*, and they concluded generally from the evidence that the organisms found in the dead mice came from the meat with which they had been fed. The conclusion was not justified, as later work of Holth (1909) and Zwick and Weichel (1910) shows. The latter authors found organisms of the Gaertner group in normal mice, and, in fact, showed that mice could be chronic carriers of organisms of the Gaertner group. The most probable explanation of the large number of positive findings obtained by Mühlens, Dahm, and Fürst, was that the Gaertner-like organisms were originally present in the intestine of the mice, probably in small numbers, and that the ingestion of, or inoculation of, the sausage-meat, etc., had increased the permeability of the intestinal wall for those organisms, with the result that apparently an auto-infection took place. A similar explanation of the early mortality in guinea-pigs inoculated with milk or milk deposits suspected to contain tubercle bacilli has been put forward by O'Brien (1911).

Zweifel (1911), working in Leipzig, examined 248 samples of raw minced meat, but found no organisms that could with certainty be assigned to the paratyphoid group. These discordant observations therefore strongly suggest a regional distribution of *B. suipestifer* (*B. paratyphosus B*).

Distribution in Man.

Bearing in mind the fact that no distinction is drawn by many German writers between *B. suipestifer* and *B. paratyphosus B*, we may now discuss the further evidence on which the ubiquity theory is based.

Conradi (1909) examined the fæces of 250 persons who had recovered from enteric fever one to ten years previously. Eight typhoid carriers (*i.e.*, 3·2 per cent.) were discovered who continued to excrete *B. typhosus* regularly, and were certainly to be classed as chronic carriers. Three of them, in fact, had been connected with the occurrence of endemic typhoid fever over many years. Eighteen of the convalescents were also found to be excreting "paratyphoid" bacilli, but in the majority of these such excretion was noted on one day only. No data are given as to differentiation.

Also, in the course of the bacteriological examination of typhoid patients, "paratyphoid" bacilli were got seven times as accidental findings, sometimes from the blood and sometimes from the excreta. Some cases (analogous to those of Busse; see p. 112) which at the post mortem presented miliary tuberculosis or pneumonia had before death excreted "paratyphoid" bacilli in the fæces or urine. The question of mixed infections of paratyphoid and other organisms, especially *B. typhosus*, has attracted the attention of numerous observers, and there appears to be good evidence that such genuine mixed infections may occur. None the less it is important to bear in mind that in all such cases the evidence put forward should be as complete as possible in the present state of knowledge. Conradi states that he had an attack of typhoid fever himself in the course of which "paratyphoid" bacilli were recovered from the blood. The fæces and urine gave exclusively typhoid bacilli, and his blood-serum agglutinated *B. typhosus* only. Other observers have recorded similar findings, and it would appear that in disordered conditions of the intestine, following infection with the typhoid bacillus, the permeability of the intestine may be so altered as to permit the entrance of other organisms into the blood-stream. The interesting fact still awaits explanation, why in such cases the organisms most liable to gain entrance in this way should belong to the Gaertner-paratyphoid group. The suggestion may at least be hazarded that these organisms have not much power of initiating infection unless present in considerable numbers, and that the path of infection has to be made easy for them by some antecedent disturbance of the intestine. Illustrative examples suggesting the occurrence of mixed infections of *B. typhosus* and *B. paratyphosus B* will be found in papers by Levy and Gaehtgens (1907), Beckers (1908), Popp (1911), and others.

Conradi was also able to isolate "paratyphoid" bacilli from the fæces and urine of four chronic typhoid carriers. As a rule these organisms were only got on one occasion. Unique findings of "paratyphoid" bacilli in fæces or urine were also made in members of apparently healthy families. With regard to foodstuffs containing these "paratyphoid" bacilli, both Conradi and Hübener stated that such could be partaken of by human beings with impunity, and that the bacilli could be recovered from the fæces, or even from the blood, on the following day, but not later. Conradi's general conclusion was that organisms of the paratyphoid group are widely distributed in Nature, so much so that to initiate any control of paratyphoid carriers was to fight against "windmills." On the other hand, Hübener (1908) made single examinations of the stools and urine of 180 people who had partaken of various sausages, with entirely negative results. Gaehtgens (1907), like Conradi, obtained positive findings of "paratyphoid" bacilli on single occasions in the excreta of a few typhoid convalescents (six) and typhoid carriers. In the former the occurrence of "paratyphoid" organisms in the stools took place in the sixth week after the beginning of the typhoid infection. Gaehtgens' conclusion, however, was not so far-reaching as Conradi's, as he believed that in two of the cases there was a genuine mixed infection, in two others the "paratyphoid" organism was acting as a mere saprophyte, while in the remaining two the suggestion was that a paratyphoid infection had succeeded the typhoid infection.

O. Mayer (1909) also performed 1,000 examinations in the neighbourhood of typhoid and paratyphoid patients, but only in two cases did he recover "paratyphoid" bacilli from the stools.

In contrast to Conradi's results entirely negative results have been obtained in other parts of Germany and in this country. Thus, working in Berlin, Sobernheim (1910) examined 1,000 samples of fæces or urine from healthy men without once finding *B. paratyphosus B.* Seiffert (1909) examined 600 samples of human fæces with negative results;

while Morgan (1905-1907), in the course of extensive researches on the intestinal flora in summer diarrhœa, failed to find *B. paratyphosus B*. Nor was Savage (1908-09) successful in finding *B. paratyphosus B* either in fæces of healthy human beings or pigs. Further, the writer, in the course of an investigation of a large series of typhoid convalescents and typhoid carriers, collected a large number of non-lactose fermenters, which gave, however, acid and gas in mannite, and handed them over to Drs. Bainbridge and O'Brien for further examination. None of the strains proved to be *B. paratyphosus B*, although several possessed cultural characters agreeing to some extent with those of the Gaertner-paratyphoid group.

Again, Bainbridge and O'Brien (1911) procured from various sources—mostly German—a number of strains (twenty-five) of "paratyphoid" bacilli. These, on examination by cultural methods, by agglutination and by absorption tests, fell into two groups—viz., one group identical with standard strains of *B. suipestifer*, and the other with standard strains of *B. paratyphosus B*. Moreover, all those strains which proved to be genuine *B. paratyphosus B* had been isolated from cases of paratyphoid fever or from paratyphoid carriers, whereas those which proved to be identical with *B. suipestifer* had been derived from foodstuffs or cases of food-poisoning. The importance of these results from the epidemiological point of view has been very clearly pointed out by Bainbridge in a recent paper before the Epidemiological Society (January 27, 1911), and it remains to be seen what amount of support will be lent to this view by future work on the subject.

With the above discussion the way is now prepared for a consideration of the excretion of the specific bacilli by the paratyphoid carrier.

IV. ON THE OCCURRENCE OF PARATYPHOID CARRIERS; FREQUENCY, SEX, ETC.

We have not yet sufficient evidence to permit us to state, with any approach to accuracy, what proportion of paratyphoid convalescents become carriers. It may be well, however, to record what data are available on the subject.

Hilgermann (1911), during four years' work in the district of Coblentz, observed 194 cases of paratyphoid fever. The incidence of the disease varied greatly in the different divisions of the district, the number of cases per division varying from 3 to 16, while in two divisions the numbers rose to 41 and 53 respectively. These latter divisions were not the most populous, and it was almost justifiable to regard them as endemic paratyphoid foci. Of the 194 cases, 92 were males and 102 were females, and they were arranged according to age groups thus :

	Number of Cases.
Under 6 years	11
6 to 14 ,,	41
15 ,, 20 ,,	55
21 ,, 30 ,,	42
31 ,, 40 ,,	23
41 ,, 50 ,,	11
51 ,, 60 ,,	5
Over 60 ,,	4
Unknown	2
Total	194

Only 53 were treated in hospital.

An interesting feature which emerged from the analysis of the cases was that a very large proportion of the attacked belonged to the upper classes of the population. Thus, 30·4 per cent. were officials, teachers, doctors, and professional men ; 15·4 per cent. were merchants ; 14·9 per cent. were engaged in agriculture ; 12·8 per cent. were in service ; while 17·0 per cent. were women and children. The classes least affected were those engaged in the manufacture and sale of foodstuffs (bakers, millers, etc.). Of the 194 cases, 7 continued to excrete the specific organisms beyond a period of ten weeks (*i.e.*, 3·6 per cent.).

A small series of 27 cases which occurred in the course of three years was observed by Gaehtgens (1907). In many of the patients the bacilli were present only during the febrile period, while in others they were demonstrable six to seven weeks after the beginning of the disease. Only one case became a chronic carrier, and, although in this person the bacilli had not been demonstrated in the stools during convalescence in 1903, they were repeatedly recovered from the urine and fæces when the control examinations were made in 1906. At the Typhoid Institute in Saarbrücken, Prigge and Sachs-Müke (1909) examined the excreta of 5,852 persons (typhoid patients, typhoid carriers, and healthy persons), and in 108 cases demonstrated the presence of paratyphoid bacilli. Of these 108 persons, 38 had clinical symptoms of paratyphoid fever, but none became carriers. The remaining 70 were classified in two groups, containing 10 and 60 persons respectively. Of the former group of 10, 3 were persons in whose neighbourhood cases of paratyphoid fever had occurred, or who had become carriers as the result of some previous paratyphoid infection; 3 were found in the neighbourhood of single cases of paratyphoid fever; while 4 were found in the course of an inquiry into a food-poisoning outbreak. The latter 4 did not remain chronic carriers, but in the other 6 the bacilli were demonstrated repeatedly. Thus, of 86 stool examinations, 72 were positive, while 37 of the 85 urine samples were positive. All 6 cases were females—viz., 3 married women in middle age, 2 unmarried women, and 1 child. The second large group of 60 cases included 16 typhoid patients, 5 typhoid carriers, and 39 healthy persons; but in these the paratyphoid bacilli were found, as a rule, only once. They have been already referred to in another section, where the similar findings of "paratyphoid" bacilli by Conradi and others are discussed. One point is of interest here, however—viz., that no case of paratyphoid fever could be brought into relation with any of these 60 occasional "paratyphoid" carriers; while of the 6 chronic carriers, 3 were believed to be the source of infection of the paratyphoid infections in their neighbourhood. It was also suggestive that these "occasional" carriers were not mainly or exclusively females, like the genuine chronic carriers. There were, in fact, 14 women, 16 men, and 25 children. As we have indicated in a previous section, the possibility has to be borne in mind that the occasional carriers were not genuine paratyphoid carriers, but merely temporary harbourers of *B. suipestifer*, perhaps contained in the food consumed.

THE VEGETATION SEATS OF THE PARATYPHOID BACILLUS IN THE BODY OF THE CARRIER.

The association of the typhoid bacillus with lesions of the gall-bladder is now a very well established fact in chronic typhoid carriers. In paratyphoid carriers, also, there is equally good evidence that the specific organisms find in the mucosa of the gall-bladder a suitable nidus for prolonged vegetation.

Forster and Kayser (1905) isolated *B. paratyphosus B* post mortem from the gall-bladder of a woman who suffered from gall-stones. Lorey (1908) also recovered the bacillus in pure culture from the gall-bladder mucosa of a carrier after the operation of cholecystectomy.

An interesting case of this kind is reported by Evers and Mühlens (1909). A woman of thirty-eight years, who three weeks previously to admission had been acutely ill with gastro-intestinal symptoms and diarrhœa, suddenly developed colic in the neighbourhood of the gall-bladder. There was extreme jaundice. No history of a previous typhoidal infection could be elicited either in her own person or in her vicinity.

Owing to the large size of the gall-bladder and considerable bleeding from the liver, cholecystotomy only was performed. A large amount of slimy, purulent fluid escaped, and a number of faceted stones. *B. paratyphosus B* was got in pure culture from the fistula fluid, and also repeatedly during the following six weeks. The blood-serum agglutinated the paratyphoid bacillus in dilution of 1 in 400, but did not agglutinate *B. typhosus*. The fæces also yielded paratyphoid bacilli on several occasions after operation, and there was no evidence that the operation had effected a bacteriological cure.

A search for typhoid carriers among 24 persons who had a history of gall-bladder trouble was made by Hamilton (1910). No fewer than 7 of these persons proved to be typhoid or paratyphoid carriers (2 typhoid carriers and 5 paratyphoid carriers). The sera of the majority of these carriers had high opsonic indices for one or other of these organisms, and agglutinated the respective organisms.

The analogy between typhoid and paratyphoid does not rest here, as in a large number of cases these organisms have been found in chronic bone abscesses, chronic periostitis, etc. Of the more recent papers on the occurrence of paratyphoid organisms in periostitic abscesses, etc., are those of Jensen and Kock (1910) and Reenstjerna (1910). An interesting account of the various situations in which the typhoid bacillus (and also, probably, the paratyphoid bacillus) may be found in association with abscess formation is given by Hess (1910), who points out that these situations have in all probability suffered some injury during the course of the initial infection, with the result that the bacillus finds there a spot of lowered resistance. It has been observed, for example, that small abscesses have formed at the sites of injection of drugs like camphor and caffeine, and that the typhoid bacillus has been recovered in pure culture therefrom. There may be doubt in some cases as to whether the real pus-producing agent is the typhoid bacillus, and not a streptococcus or a staphylococcus, but in any case there are numerous instances in which *B. typhosus* is the only organism that can be recovered.

Urinary carriers of *B. paratyphosus B*, like those of *B. typhosus*, have not yet been observed, but there is little doubt that such occur. The organism has frequently been recovered from the urine, and it is not unlikely that, like *B. typhosus*, the paratyphoid organism finds a nidus for vegetation in the various recesses of the urinary tract. Gould and Qualls (1912) have, indeed, recovered *B. paratyphosus A* from the prostatic secretion, as well as from the blood, in a case of paratyphoid fever due to this organism.

AUTO-INFECTION IN PARATYPHOID CARRIERS.

As in the typhoid carrier, so also in the paratyphoid carrier evidence is forthcoming suggesting that auto-infection may occur. Prigge and Sachs-Müke (1909) record two interesting cases of this sort. One was a girl who, in autumn, 1906, while nursing a small child suffering from paratyphoid fever, was found to be a carrier. For two years she came regularly to the Institute, and almost on every occasion the excreta were positive. In the spring of 1908 she had an attack of bronchitis, with rise of temperature to 39·3° C., and the physician, suspecting tuberculosis, sent a sample of sputum for examination. No tubercle bacilli were present, but paratyphoid bacilli were demonstrated beyond all doubt. In the course of ten days the temperature returned to normal. It may be noted here that pulmonary complications in the course of paratyphoid fever are not infrequent.

Another woman observed by the same authors was found to be passing paratyphoid bacilli in her stools during a paratyphoid outbreak. She stated, however, that she had not been ill. Her serum gave a positive Widal reaction for paratyphoid. After three negative examinations in the course of three months, she was struck off the list of carriers ; but in the following month she had a severe attack of paratyphoid fever, and during the whole course of the infection the bacilli were demonstrated in the stools and urine. After recovery the bacilli disappeared completely during several months' observation, but again returned.

INSTANCES OF INFECTIVITY OF PARATYPHOID CARRIERS.

The evidence available on this subject is as yet not nearly so extensive as in the case of the typhoid carrier, and much of that evidence is not so complete on the bacteriological side as one would wish. The thorough working-out of a paratyphoid epidemic, and the incrimination of carriers in connection therewith, involves much laborious and difficult bacteriological research, the facilities for which are not always available. The instances we propose to adduce, though not entirely satisfactory, afford very strong presumptive evidence of the infectivity of the paratyphoid carrier.

In September, 1907, an outbreak reported by Konrich (1907) took place in the children's ward of a surgical clinic. Three of the forty-four patients took ill with high fever and severe abdominal pains. Other and more numerous cases had headache and diarrhœa, with gradual rise of temperature, but no acute symptoms. Rose spots were present in some of the cases, and the attacks lasted as a rule about ten days. In eleven of the cases *B. paratyphosus B* was isolated from the blood. The following evidence was obtained which threw light on the causation of the outbreak:

On August 5 a child had been brought into the clinic suffering from rickets. A few days later this child developed fever and diarrhœa. In the course of the examination of the stools of the affected children, this child's excreta were also examined, and the paratyphoid organism recovered. It was also recovered on four occasions in the course of the next fortnight. Also, the blood of this child taken on the fortieth day after the beginning of the disease agglutinated *B. paratyphosus B* in a dilution of 1 in 100. The probability, therefore, was that the child had come into hospital already infected. Accordingly, eleven out of eighteen persons from whose house the child had come (in a neighbouring town) were examined, and four of them (viz., a brother and sister of the child and two members of another family with whom there was frequent social intercourse) were found to be excreting *B. paratyphosus B* in their stools. According to their own account and that of the neighbours, these carriers had not been ill during the past year, and the examination of their excreta was made while the child was still in hospital. Further details are, unfortunately, wanting.

Hilgermann (1911), to whom we are indebted for much information on the occurrence of paratyphoid fever, mentions a few groups of cases in which inquiry elicited presumptive evidence only of the presence of a paratyphoid carrier as the source of infection. The chain of evidence was broken by absence of bacteriological support, and the evidence rested mainly on the fact that cases had had intercourse with persons who either had recovered some time previously from paratyphoid fever, or who had come from an infected area.

Evers and Mühlens (1909), whose case of paratyphoidal cholelithiasis is mentioned in another section, observed another case of paratyphoid infection in the same hospital, which they believed was directly infected from this case. The person attacked was a woman of forty-three years, who, after being in hospital for a fortnight suffering from carcinoma mammæ, developed acute fever. From the blood *B. paratyphosus B* was isolated. Eight days later the same organism was recovered from the fæces, and the blood agglutinated *B. paratyphosus B* in a dilution of 1 in 150.

The etiology of this acute paratyphoid infection was thus explained by Evers and Mühlens. The woman had lain in the same room with the case of paratyphoidal cholecystitis before the exact nature of the latter case had been discovered by bacteriological examination. A possible mode of infection was an enema syringe which had been used in both cases. This had certainly been washed, but not disinfected.

Sacquépée and Bellot (1910) report a very interesting paratyphoid outbreak in a military corps consisting of 250 men. In June, 1909, 19 cases occurred in this corps in the course of eight days. Thus—

1st case	fell sick	on June	14.
2 cases	,,	,,	15.
5 ,,	,,	,,	16.
5 ,,	,,	,,	18.
3 ,,	,,	,,	19.
2 ,,	,,	,,	20.
1 case	,,	,,	21.

The cases were not severe, and the duration was not more than fifteen to twenty-two days. There were no fatalities. Of the

19 attacked, 4 only were really seriously ill, with marked prostration and delirium. *B. paratyphosus B* was recovered from the blood in 7 out of 8 cases examined, from the fæces in 10 out of 12 cases, and from the urine in 2 out of 12 cases. The sera of the cases agglutinated *B. paratyphosus B* in dilutions varying from 1 in 350 to 1 in 900, and had no action on *B. typhosus* or *B. paratyphosus A*. As a source of infection water could be excluded, and it remained to be determined whether contaminated food would afford a reasonable explanation of the outbreak. It was found that an assistant cook who had been in the kitchen for several months had been attacked a little before the epidemic explosion by some slight malady which was not definitely diagnosed. He had been admitted to the hospital, and was discharged convalescent. This cook, on being recalled and questioned, stated that some days before June 10 he was indisposed with headache and anorexia. He had nevertheless continued his service in the kitchen, and must have contaminated the food. *B. paratyphosus B* was repeatedly found in his stools in August, September, and October, and his serum agglutinated *B. paratyphosus B* in dilutions of 1 in 80. It did not agglutinate *B. typhosus* or *B. paratyphosus A*. In all probability, therefore, the outbreak was due to food contaminated by a paratyphoid carrier who had passed through an abortive attack of the fever.

Two outbreaks of paratyphoid infection in this country have recently been reported. In that described by Bainbridge and Dudfield (1911), and which occurred in a boarding-house, the symptoms were mainly those of acute gastro-enteritis, and the *B. paratyphosus B* was isolated from the fæces of several affected cases, and thoroughly identified as such by agglutination and absorption tests. The sera of the cases also agglutinated this organism in dilutions varying from 1 in 100 to 1 in 400. The question of contaminated food was very carefully inquired into, but it was found that no one article of food had been partaken of by all the persons affected, and that therefore the most probable source of infection was a paratyphoid carrier. Suspicion fell on a servant who had entered the boarding-house a few days before the outbreak occurred, and who had remained at work during the outbreak, although she had a mild attack of diarrhœa. The excreta of this woman were not found to contain *B. paratyphosus B*, but her blood-serum, even four months after the outbreak agglutinated *B. paratyphosus B* in a dilution of 1 in 100. The difficulty of obtaining samples of blood and excreta from other persons in the boarding-house, who might probably have been carriers, rendered a complete investigation of the outbreak impossible.

A food-poisoning outbreak at Wrexham in 1910 was reported in its clinical and bacteriological aspects by W. R. Smith (1910), Williams (1910), and Tromsdorff, Rajchmann and Porter (1911). The food which caused the infection was pork-pies, which had been obtained by the victims from the same bakery. *B. paratyphosus B* was recovered not only from the pies, but also from the blood and organs of a fatal case. The blood-serum of numerous cases also agglutinated this organism. It was ascertained, however, that the pig from which the pies had been made was a perfectly sound animal, and pies from the same animal had been prepared in other bakeries and consumed without ill effect. Suspicion therefore fell on the bakery itself. The serum of five employees in the bakery was tested, and in two a positive result was obtained. One of these persons had eaten some of the pies. The other, a female and the head-cook, had not partaken of the pies, but from her fæces and urine the *B. paratyphosus B* was recovered. The conclusion therefore was that the infections owed their origin to food contaminated by a paratyphoid carrier.

B. Suipestifer and B. Enteritidis Gaertner from the Carrier Point of View.

It would be outside the scope of this work to discuss the relationship of these organisms to outbreaks of food-poisoning. The subject has been very fully dealt with by Bainbridge in his recent Milroy Lectures (1912), and to these the reader must be referred.

A consideration of all the evidence adduced with regard to the distribution of *B. suipestifer* in Nature permits the conclusion that this organism is certainly a cause of food-poisoning, and that the meat most frequently responsible in food-poisoning outbreaks due to this organism has been derived from the pig. It would appear, also, that such meat has become contaminated by the *B. suipestifer* after the slaughter of the animal, probably by contact with the intestinal contents, which in certain districts undoubtedly harbour this organism. That healthy pigs harbour this organism in their intestines is clear, but all the German and English evidence goes to show that it is only in pigs belonging to certain districts that this vegetation can be considered common. Even in outbreaks of swine fever this organism is by no means invariably associated with the filter-passing virus which is the essential cause of the disease.

The occurrence of *B. suipestifer* in the intestinal canal of healthy man is also in all probability regional, and doubtless correlated with the consumption of food containing these organisms in small numbers.

That the *B. suipestifer* found by certain observers in apparently wholesome foodstuffs does not more frequently initiate infection is most likely due to the fact that only a very small number of micro-organisms are in such cases present in the food as ascertained by direct plating, and indeed special methods, such as the preliminary digestion of the meat with papayotin, may have to be employed to demonstrate them.

The *B. suipestifer* has also been found in certain cases of summer diarrhœa of children (Williams, Murray and Rundle, 1910). The writer observed a very severe and fatal case of enteritis in a child due to *B. suipestifer*, which was recovered at autopsy from the intestine and spleen, and fully identified by agglutination and absorption tests. The whole of the intestinal mucosa had a purplish velvety appearance, and microscopically there was an enormous hyperplasia of the lymphoid apparatus, but no ulceration. In this case there was no reason to incriminate foodstuffs, but it was certainly of some interest that in another healthy member of the family from which the child had come to hospital the same organism was recovered from the fæces. Although, therefore, in the recorded outbreaks of food-poisoning associated with *B. suipestifer*, there is practically no evidence pointing to the contamination of food by human carriers of this organism, or suggesting the likelihood that human chronic carriers of *B. suipestifer* really occur, the question must still be considered as undecided, and further evidence must be awaited.

With regard to the distribution of *B. enteritidis Gaertner*, much less difficulty is experienced in weighing up the evidence, as this organism can generally be identified with little trouble provided specific antisera are available. The association of this organism with outbreaks of food-poisoning in which the food has been derived mainly from cattle is discussed fully by Bainbridge, and the only relevant matters germane to this work are those dealing with its occurrence in the intestinal tract of man apart from outbreaks of food-poisoning. It is only in rare cases that *B. enteritidis Gaertner* has been recovered from the fæces of healthy persons, and there is no direct evidence that, after an attack of food-poisoning, this organism continues to vegetate in the intestinal canal. In an exceedingly well-described outbreak of food-poisoning due to *B. enteritidis Gaertner* at St. Johann, Rimpau (1910) recovered the organism from the fæces in 53 out of 102 cases (*i.e.*, 51·9 per cent.), and in 91 per cent. of the cases examined, within the first week after the outbreak commenced. In three cases only were the stools positive in the fourth week, and none of the attacked became chronic carriers. Recently, however, G. Dean (1911) has recorded an undoubted carrier case. This was a woman of sixty-one years, who was operated on for cholecystitis. There was no history of an attack of acute food-poisoning, but the gall-bladder trouble dated from ten years back. *B. enteritidis Gaertner* was recovered from the pus in the gall-bladder, from the interior of the gall-stones, and also from the fæces, and was identified as such by rigorous tests.

This case would therefore constitute an exact parallel to the typhoidal and paratyphoidal cholelithiases in chronic carriers, and in the light of this case one cannot afford to ignore the possibility that food may become contaminated, or contact cases produced, by a chronic carrier of *B. enteritidis Gaertner*.*

V. PARATYPHOID A.—INFECTIONS AND PARATYPHOID A.—CARRIERS

During the past two years a considerable amount of attention has been devoted to the study of certain pyrexias occurring in India associated with *B. paratyphosus A*. In the course of the inquiry into the occurrence of enteric fever in India (1906-1908, Semple and Greig), four cases were proved bacteriologically to be due to infection by *B. paratyphosus A*, and two only to *B. paratyphosus B*.

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* The writer has also recently (July, 1912) obtained cognizance of two as yet unpublished cases of chronic urinary infection with B. *enteritidis Gaertner*.

Since that time our knowledge of paratyphoid A fever has been considerably increased by the work of army medical officers in India, and it would appear that in that country the paratyphoid A organism, which in Europe and America is only rarely met with, is a frequent cause of typhoidal disease. Paratyphoid fever is, in fact, defined by Grattan and Wood (1911) as an acute septicæmic fever due to the presence in the blood of *B. paratyphosus A*, and in a recent paper by Firth (1911), this view is strongly upheld. These authors state that the findings of the B variety in India are very few, and not free from criticism. The A bacillus alone would, according to Firth, play the causative rôle in paratyphoid fever in India, and he would further suggest that in other countries the B variety may not be the cause of genuine paratyphoid fever, but only of acute gastro-enteritis. It may be said at once that there is no evidence in support of this latter extreme view. In Europe the association of *B. paratyphosus B*, not only with paratyphoid fever, but occasionally also with gastro-enteritis, has been abundantly established on firm bacteriological foundations. Indeed, since the publication of Firth's paper towards the end of 1911, Babington (1912) has reported on an outbreak of paratyphoid B fever in the 1st Battalion of the Suffolk Regiment at Malta. There were fourteen cases, and in seven a diagnosis was made by blood-culture. The organism recovered from the blood was certified as a genuine *B. paratyphosus B*, not only by the author, but also by Cummins, of the Royal Army Medical College, to whom a subculture was sent.

CLINICAL FEATURES OF PARATYPHOID A. FEVER.

It may be of interest to detail some of the clinical features noted in the various outbreaks described by workers in India. In 1910 Harvey observed a number of cases in which the paratyphoid A organism was recovered from the blood or excreta. In all cases severe frontal headache was the rule in the early stages of the fever, and this might be accompanied by pain in the back of the neck or in the lumbar region. The mental condition was clear in all. Diarrhœa was sometimes present. In another series of eight cases observed by Grattan and Harvey (1911), constipation was the rule, and all the patients suffered from sore throat. A more complete account of the clinical manifestations of paratyphoid A fever in India appears in an excellent paper by Grattan and Wood (1911).

According to these authors, the onset of the fever is gradual, with severe frontal headache and pains in the back and limbs. About half of the cases are accompanied by bronchitis and sore throat. The temperature rises in staircase fashion, reaching its maximum by the fifth or seventh day. The highest points reached are 102·5° to 103·5° F., and a normal temperature is reached about the ninth to the fourteenth day. A rash is not so common as in enteric fever, and may be morbilliform, erythematous, or purpuric, in character. Constipation is the rule, and there is occasional epistaxis. Severe types of the disease are clinically indistinguishable from enteric fever, and the pyrexia may last from twenty-one to thirty-six days, but the convalescence is more rapid. Relapses are common, and are often ushered in by a sudden rise of temperature and tenderness over the gall-bladder. Cholecystitis is not uncommon, also pneumonia and bronchitis.

An anæmia quite out of proportion to the severity of the disease is often produced. The average incubation period, according to Grattan and Wood, is fifteen days.

Baermann and Eckersdorff (1909) observed eight cases of paratyphoid A fever in Sumatra, the organism being obtained by blood-cultures in two cases out of six. The onset in all cases was accompanied by diarrhœa.

ISOLATION OF THE ORGANISM FROM CASES OF PARATYPHOID A.—INFECTION.

In a large proportion of the Indian cases *B. paratyphosus A* has been isolated from the blood and from the fæces. Isolation from the fæces only cannot be held to constitute conclusive evidence of paratyphoid A infection, unless the organism so isolated has been thoroughly identified by rigorous serological tests. Bacilli culturally identical with *B. paratyphosus A* were found in normal fæces by Morgan (1906-07), who showed, however, that they were not agglutinable by specific paratyphoid A antiserum. It is important, therefore, to have at hand a quantity of specific antiserum for agglutination purposes, and also, if considered necessary, for absorption experiments.

With regard to the agglutinin content of the patient's sera, Harvey (1910) noted that *B. typhosus* was agglutinated in somewhat higher dilution than *B. paratyphosus A*, but that the reaction to the latter organism occurred first in the tubes. The titres as a rule were low—1 in 20 to 1 in 40. According to Grattan and Wood, agglutinins for *B. paratyphosus A* do not appear much before the twelfth day, reach their height about the twenty-fourth day and disappear within two months. The fact that typhoid vaccination has been practised on Indian troops has to be taken into consideration in estimating the value of the agglutinin reaction in paratyphoid A fever, and absorption experiments have to be performed. In the Sumatra cases very much higher agglutinin titres were obtained—viz., 1 in 160 to 1 in 400.

B. PARATYPHOSUS A AND THE GALL-BLADDER.

Cholecystitis has been shown to be a not uncommon complication of paratyphoid A fever, and in several instances the organism has been recovered from the gall-bladder, either at operation or in the few recorded autopsies. Thus, Blackwell (1911) recovered the organism from the gall-bladder in a fatal case of paratyphoid A infection in India. At St. Thomas's Hospital, Windsor (1911) also recovered a similar organism at post mortem from the gall-bladder of a man of fifty-four years, who had suffered from biliary colic. The strain isolated was culturally identical with *B. paratyphosus A*, but no confirmatory test was made with specific antiserum.

Similar discoveries of *B. paratyphosus A* in the gall-bladder have been made by Blumenthal (1904), Forster and Kayser (1905), and more recently by Springer (1911). The latter's case was a female of sixty-eight years, who had never had typhoid fever or any similar affection. Thirty years previously she had suffered for a prolonged period from gall-stone colic, but in recent years she had not been troubled in this way. At the operation the gall-bladder was found to be full of stones, and there was a carcinoma at the opening of the ductus choledochus into the duodenum. The bacillus was agglutinated by the patient's serum in a dilution of 1 in 800. The same organism has also been found in certain abscess formations (Gwyn, 1889: Aoki, 1910), in paratyphoid A carriers, and also as the specific cause of a form of chronic enteritis (Bandi, 1909).

EXCRETION OF THE SPECIFIC ORGANISMS BY THE PARATYPHOID A.—CONVALESCENT.

At the enteric fever depot in Naini Tal, 10 out of 157 convalescent paratyphoid cases continued to excrete the bacilli for some time after recovery, but one only remained infective for a period longer than three months. This person, in fact, ceased to carry within five months. It is the experience of workers in India that convalescent or " acute " paratyphoid A carriers are common, and, further, that the mildness of the attack in some cases renders them liable to be overlooked. Grattan and Wood believe that epidemics are started by acute carriers whose illness has not been recognized. These acute carriers infect other men, some of whom are recognized as cases of paratyphoid A infection, while others are not so diagnosed. The latter return to barracks, and again disseminate infection.

ASSOCIATION OF PARATYPHOID A.—CARRIERS WITH OUTBREAKS OF THE DISEASE.

Inquiries into these outbreaks of paratyphoid A fever have yielded evidence pointing clearly to the implication of carriers as the sources of infection. Thus, in the small outbreak of nine cases at Manora Camp during August to October, 1911, Grattan and Harvey (1911*a*) discovered that a certain Private K. arrived at the camp from furlough on July 15. Three days later he was admitted to hospital for pyrexia of uncertain origin. The disease ran a mild febrile course, and he was discharged on August 5.

The first case of paratyphoid A fever was admitted on August 20, from the barrack-room in which this Private K. lived. K. was accordingly sent for, and his serum was found to agglutinate *B. paratyphosus A.* He was therefore readmitted on September 30, and the last case occurred about October 12. K. on arrival at the Naini Tal depot on October 20 was found to be suffering from anæmic headaches, and the patient stated that when in hospital he had suffered from abdominal pain over the right hypochondrium.

On October 25 the fæces were found to contain *B. paratyphosus A* practically in pure culture, and up to November 11 his fæces continued to yield this organism daily, when the excretion suddenly ceased, all subsequent examinations being negative. In another series of cases observed by the same authors (1911*b*) the suggestion was that the source of infection was a cook who had passed through an irregular fever, in which his blood serum agglutinated *B. paratyphosus A* up to 1 in 200. Within six weeks of his discharge from hospital, this man was employed in connection with the food-supply of the camp, and it was notable that the first two cases which occurred in the camp lived in the same tent with this man. Unfortunately, it was never proved bacteriologically that this man was a chronic carrier.

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CHAPTER IV

DIPHTHERIA

I. HISTORY AND INTRODUCTION.

BEFORE the discovery of the diphtheria bacillus, and even before the science of bacteriology had been founded, it was believed on clinical grounds by physicians (Trousseau, 1868) that severe cases of diphtheria could give rise by infection to mild cases of " erythematous sore throat," and these in turn to fresh cases of membranous diphtheria. Later, it was also recognized on clinical grounds that patients who had recovered from an attack of diphtheria, and who had seemed perfectly well for two or three weeks, could still communicate the disease to others (Bristowe, 1884). In 1883 Klebs described the diphtheria bacillus as occurring in the false membrane from diphtheria patients, and in 1884 Loeffler published the account of his successful attempts to cultivate this bacillus, and of his experiments which demonstrated its pathogenicity for animals. In Loeffler's first description of his researches on the *Bacillus diphtheriae,* he recorded the fact that one of the virulent strains which he had isolated came from the throat of a perfectly healthy person.

The clinical and bacteriological evidence, therefore, both pointed to the existence of persons who were the carriers of the *B. diphtheriae,* but who were themselves in normal health, either having recently recovered from an attack of diphtheria or having been in sufficiently close contact with cases of the disease to be invaded by the bacillus, but without themselves suffering from any local pathological change.

The transmission of the contagion by persons in health, which had been suspected on clinical grounds, thus received powerful support when the hypothetical *materies morbi* became known as the *Bacillus diphtheriae.* However, the pathogenicity of the diphtheria bacillus was not yet very firmly established, and these earlier observations on its occurrence in healthy persons tended to foster a general feeling of scepticism with regard to the pathogenic properties of this bacillus.

After some years of delay, the accumulation of a long series of observations made it no longer possible to refuse to accept the bacillus as the cause of diphtheria, or to recognize the part which healthy carriers played in the spread of the disease.

In 1889-90 Roux and Yersin (1890) found the *B. diphtheriae* in the throat of a healthy person who had recently suffered from diphtheria, two weeks after the membrane had disappeared, and about the same time Loeffler (1890) recorded the occurrence of the *B. diphtheriae* in the throat of a diphtheria convalescent three weeks after the temperature had returned to normal. He also found the bacillus in cases of mild sore throat. At one time attention was distracted from the importance of carriers by the view put forward by v. Behring (1901) and others that the *B. diphtheriae*, though undoubtedly the causal organism in diphtheria, was ubiquitous, and therefore that precautions taken to avoid it were useless.

At that time, however, communities which were free from diphtheria had not been systematically examined bacteriologically and compared with others in which cases of diphtheria had recently occurred. The confusion which then existed between the *B. diphtheriae* and the pseudo-diphtheria bacillus of Hofmann lent support to the idea of ubiquity.

The importance of the healthy carrier as a factor in the epidemiology of diphtheria is now generally recognized. This conclusion is based at the present time on the large accumulation of recorded facts concerning the occurrence of the *B. diphtheriae* and the spread of the disease, and the close association of carriers of the *B. diphtheriae* with outbreaks of diphtheria.

Sacquépée (1910) has recently advocated a view which has a certain number of supporters, especially in France. According to this conception of the bacteriology and epidemiology of diphtheria, carriers play an important part in disseminating the disease, but are of different degrees of importance according to the degree of virulence of the bacillus which has invaded the carrier's mucous membrane. The view of Sacquépée and those whom he represents appears to be that all varieties of the bacillus occur from the completely non-virulent Hofmann's bacillus to very highly virulent varieties of *B. diphtheriae*, and that all these strains are really *B. diphtheriae*, and change their virulence from time to time in the different human subjects which they inhabit. Sacquépée considers that spontaneous epidemics of diphtheria sometimes arise on account of a strain of Hofmann's bacillus having acquired virulence. This view does not appear to be supported by most of the known facts.

CAUSATION OF DIPHTHERIA BY THE B. DIPHTHERIAE.

The validity of the argument as to the efficacy of " carriers " necessarily rests on the firm ground of the universally accepted efficacy of the *B. diphtheriae* to cause the disease under suitable circumstances, and the absence of the disease apart from the bacillus.

The evidence for the causation of diphtheria by the *B. diphtheriae* may be briefly summed up as follows :

1. The *B. diphtheriae* is closely associated with diphtheria. In about 70 per cent. of cases clinically diagnosed as diphtheria the *B. diphtheriae* has been found at the time of examination.
2. The *B. diphtheriae* occurs very infrequently in communities of healthy persons, or in persons who are not in close relation with cases of diphtheria.
3. Pure cultures of *B. diphtheriae* can be made to communicate to guinea-pigs a disease which is very similar to diphtheria in man. The resemblance includes local fibrinous exudation at the seat of inoculation, fatty degeneration of the heart and liver, and paralysis referable to disease of the central nervous system and nerve fibres.
4. Antitoxic serum prepared by injecting horses with the toxin formed in pure cultures of *B. diphtheriae* has a remarkable curative and preventive action on the disease in man, and also in experimental animals.

Many epidemics have been traced to the introduction of a " carrier " into a community, and in some of these cases careful examination of the circumstances scarcely leaves room for doubt that the migration of the disease was due to a change of residence of persons who were known to harbour *B. diphtheriae*. In other instances the spread of the disease has been found to be associated with previously unrecognized carriers, and to have ceased when they were isolated. It is therefore now generally acknowledged that the carriers of the *B. diphtheriae* are a source of danger to the community.

CARRIERS OF THE DIPHTHERIA BACILLUS.

Carriers may be divided into three classes :

Class I. Convalescent Carriers—i.e., those who have had diphtheria and in whom, after an apparent return to health and the disappearance of the local membrane or exudate, the *B. diphtheriae* is still found.

This class may be again divided into those who on close examination appear to be in perfect health, and those who do not. This distinction is not an easy one to maintain in practice, since convalescents with large tonsils and adenoids, or with chronic catarrh, appear to be especially liable to harbour the bacillus. A further subdivision, consisting of those who have only had a slight sore throat, unrecognized at the time as diphtheria, is of theoretical importance, but for practical purposes these carriers must be included in the next class.

Class II. is made up of those who have had no attack of diphtheria which was recognized as such, but who are found to yield the *B. diphtheriae* on examination. These correspond to the "*Bazillenträger*" of German writers, or "*healthy carriers*."

Class III. consists of *chronic carriers*, who may be defined as those who are known to have harboured the bacillus for more than three months. Some of these persons present no obvious pathological changes, but most of them probably suffer from an unhealthy condition of the mucous membrane of the nasopharynx, nose, or middle ear. Some of them may have had a chronic infection of the antrum of Highmore, or other accessory cavity of the nose; others have chronic tonsilitis, laryngitis, or fibrinous rhinitis. The infection in these cases of chronic diphtheria may last a very long time. The bacillus may indeed be recoverable either continuously or intermittently for as long as three years or more.

The spread of diphtheria by carriers will be dealt with in these pages under the following headings :

Section II.—The bacteriology of diphtheria, including means for the detection of the *B. diphtheriae* and its differentiation from other bacteria.

Section III.—The occurrence of the *B. diphtheriae* and its distribution in the general population and infected communities.

Also reference will be made to the sites in which it occurs in the human body, and the occurrence of *B. diphtheriae* in the lower animals and elsewhere apart from man.

Section IV. — The persistence of the *B. diphtheriae* in carriers.

Section V.—The infectivity of the *B. diphtheriae,* including the evidence as to the spread of the disease from patient to patient directly or by intermediaries, and the means by which the bacillus is transported from one person to another.

Section VI.—Pathogenesis of carrier state and immunity.

Section VII.—The treatment of carriers with the object of promoting the disappearance of the bacillus, considered from the point of view of the individual.

Section VIII.—The public health measures aimed at preventing the distribution of the disease by carriers.

II. BACTERIOLOGY.

Before considering the evidence as to the distribution of the *B. diphtheriae* and its occurrence in "carriers," a short account must be given of the means employed to detect its presence and the criteria considered necessary for its identification.

The group of micro-organisms to which the *B. diphtheriae* belongs includes a considerable number of allied forms, which are known as "diphtheroid bacilli."

The members of this group are non-motile, Gram-positive, and non-sporing bacilli, which are distinguished by their growth as diplobacilli, tending to become segmented and clubbed on culture media, and also by their parallel or **V**-shaped arrangement (when seen in dried and stained films), which last peculiarity is probably due to their manner of division.

The only diphtheroid bacilli which it will be necessary to consider in the present work are those which occur in the throat, nose, and ear of man, and which, in young cultures on solidified serum, present some morphological resemblance to the *B. diphtheriae.*

Other members of the group occur commonly on the human skin, urethra, etc., but these are seldom a cause of difficulty in the diagnosis of the diphtheria bacillus.

The morphological appearance in stained films from a young six- to eighteen-hour serum culture is the test most commonly and most satisfactorily employed for the detection of the diphtheria bacillus in routine examinations.

A more exact and certain identification of any strain can only be carried out after the bacillus has been obtained in pure culture. The most serviceable classification of this group of bacilli is that introduced by Park and Beebe (1894) and adopted by Graham-Smith (1908*a*). It is based on the fermentation of glucose and on the virulence test for the guinea-pig.

By making use of the additional test of the fermentation of cane-sugar (Knapp, 1904, and Graham-Smith, 1908*b*), the differentiation may with advantage be carried further. The fermentation of other carbohydrates is not of much value for this purpose.

The group, then, is subdivided in the following manner:

1. Those bacilli which do not form acid in glucose media. These are non-virulent (Hofmann's bacillus).

2. Those which form acid from glucose, but not from cane-sugar:

(1) Virulent for guinea-pigs (*B. diphtheriae*).

(2) Non-virulent (non-virulent *B. diphtheriae*, *B. maculatus* of Graham-Smith, *B. coryzae segmentosus*).

3. Those which form acid from glucose and from cane-sugar (*B. xerosis*).

METHODS.

Routine examination for the presence of the *B. diphtheriae* is carried out by some one or other modification of the well-known technique produced by Loeffler. A sterile cotton-wool swab is rubbed carefully over the tonsil or part suspected of infection, and is immediately, or after the lapse of twenty-four hours or even longer in the case of specimens sent by post, rubbed firmly and repeatedly over the surface of a selective solid serum culture medium.

This medium may be prepared, according to Loeffler's original method, by slowly coagulating and inspissating in sloped tubes a mixture of three parts of serum and one part of broth containing

2 per cent. of glucose, or by simply coagulating serum at 60° to 70° C. without the addition of glucose-broth.

Horse, ox, or sheep serum may be used, but it is important that the resulting medium should be firm in consistency and not easily broken up by vigorous application of the swab to its surface.

Myer Coplans (1911) has recently introduced a modification of Loeffler's medium containing in addition 1 per cent. sulphocyanide of potassium and 1 per cent. of neutral red. He claims for this medium the advantage that the colonies of the *B. diphtheriae* may be recognized at once from those of any other organism by the peculiar red tint produced by them in the surrounding medium. Rankin (1911) has used this medium in the examination of 3,000 swabs for purposes of diagnosis, and strongly recommends it, but it has not yet been thoroughly tested elsewhere.

Whichever of the serum-media are used, it is a decided advantage for the worker to keep as far as possible to one kind of medium for purposes of diagnosis, so that he may be thoroughly familiar with the morphology of the organisms met with on this particular medium. He should, moreover, from time to time check the correctness of his conclusions by isolating the bacilli and testing them further.

MORPHOLOGY.

After the serum slopes have been inoculated, the cultures are incubated at 35° to 37° C. for six to eighteen hours, and films are then made and examined microscopically. At the end of six hours' incubation the bacilli can often be recognized, but a negative diagnosis should never be made without an examination of the culture after eighteen hours' incubation.

A further examination of the culture after thirty-six or forty-eight hours is practised by some bacteriologists on the ground that by this means a large increase of the "positive" results is obtained, especially in the case of convalescents and carriers. By this time, however, the morphology of some of the diphtheroid bacilli has much more nearly approached that of true *B. diphtheriae,* and the increase in the number of positive results may in part be due to the mistaken inclusion of some of these forms.

Some bacteriologists prefer to make films from several separate colonies of suspicious appearance, but probably the best method is to make a film with material obtained by scraping all over the surface of the culture. By this means the inclusion of *B. diphtheriae* is best assured, even if only very few colonies are present. The *B. diphtheriae* is usually readily recognized in films from young serum cultures by its characteristic arrangement and morphology. It is unnecessary here to describe in detail the forms of the *B. diphtheriae* met with, as these are so well known and have been frequently and thoroughly described. Full descriptions and figures are given by Wesbrook, Wilson, and McDaniel (1900), and by Graham-Smith (1908*c*).

It is important, however, to remember that the *B. diphtheriae* is very varied in its morphological appearance.

It will be sufficient to mention here that the *B. diphtheriae* from a young serum culture when stained by Loeffler's methylene blue is chiefly characterized by a tendency to segmentation in an uneven manner, by variability in size and form in the same film, or even in the same field of the microscope, and by a characteristic arrangement of the bacilli in groups. The short, solid variety and that known as the "sheath" variety are perhaps the most liable to escape recognition. The appearance of polar granules, especially when Neisser's stain is used, is usually very characteristic, but these granules may be absent, and they often occur in certain diphtheroid bacilli, and occasionally in Hofmann's bacillus. Neisser's stain is therefore only exceptionally useful as an aid to diagnosis. A film stained by Gram's method is of great value in some cases of uncertainty.

The *B. diphtheriae,* when assuming its common forms, is very readily recognized, but some of the less usual varieties are occasionally liable to confusion with certain non-virulent diphtheroids which will be mentioned later. Uncertainty is especially liable to occur when only few bacilli are present in the stained film, and the typical arrangement is not seen.

For the routine diagnosis of the *B. diphtheriae* the morphological examination as described above is usually quite sufficient. Further accuracy in identification is only necessary (1) when for any reason the correctness of the diagnosis is uncertain on account of unusual microscopical morphology or the naked-eye character of the growth on culture media ; (2) in the case of cultures from chronic carriers, when the question of prolonged isolation of the patient makes it advisable to confirm the diagnosis in every possible way ; (3) in the case of cultures from the ear. (4) In order to test the morphological standard of the observer, it is extremely desirable that he should isolate strains occasionally. The diagnosis by morphology has a certain small subjective personal element, which it is of advantage to control in this way.

Isolation of the Bacillus.

Pure cultures are necessary in order to examine the action of the bacillus on carbohydrates and for testing its virulence.

Isolation is best carried out by plating from a young serum culture on serum-agar (serum, 1 part; agar, 9 parts). The appearance of colonies of diphtheria bacilli varies very much, but the most typical form is a small, semi-translucent, but not quite circular colony, of a texture which appears coarsely granular under a low power of the microscope. The colonies are usually most easily recognized and picked off the plates after two days' incubation.

The morphology of the *B. diphtheriae* when a film is made from a young colony on an agar plate is often so like that of a streptococcus that an inexperienced observer might fail to recognize its bacillary nature. From serum-agar the films are more characteristic.

Sugar Tests.

The sugar tests are probably best carried out by inoculating test-tubes containing 2 per cent. peptone water or the serum water of Hiss, with the addition of 1 per cent. of the sugar, and incubating the cultures at 35° to 37° C. for two to three days.

The rapidity of acid production varies, but the litmus has almost always changed colour after incubation for forty-eight hours, when glucose is fermented by the bacillus under examination. German observers as a rule appear to prefer a serum-agar medium to which litmus and 1 per cent. of the sugar has been added.

In addition to the above cultural tests the appearance of cultures on serum-agar and broth is of considerable diagnostic value.

Test for Virulence.

The virulence of a strain is tested by injecting 2 or 2·5 c.c. of a two days' broth culture which has been grown at 35° to 37° C., and which has not developed an acid reaction, subcutaneously into a guinea-pig of 200 to 300 grammes weight, and into a similar animal 2·5 to 3·0 c.c. of the same culture, with the addition of 0·5 cc. of diphtheria antitoxin (about 250 antitoxin units).

In the case of a strain of true virulent *B. diphtheriae* the guinea-pig which has been injected with culture alone dies in two to five days with typical post-mortem appearances, while the animal which has also received antitoxin remains well, with hardly any local swelling.

It is essential that the broth culture used for testing virulence should be pure, as in the case of impurity the test may be spoilt either by the contaminating organisms proving fatal to the guinea-pig, or by their presence inhibiting the growth of the *B. diphtheriae*, or destroying the toxin formed by it, in which case the guinea-pig may survive.

Strains of diphtheroid bacilli which are able to kill a guinea-pig are sometimes met with, but in their case antitoxin has no protective action. Such strains have been described by Rüdiger (1903) and others.

True specific virulence for the guinea-pig, as demonstrated by animal experiments carried out in the manner described above, is a complete proof that the strain of bacillus tested is a true *B. diphtheriae*, and this is the only absolutely certain test available.

The question has been raised from time to time whether virulence for the guinea-pig is a correct test of virulence for man. The diseases in the two cases appear to be very similar. In both man and the guinea-pig the bacilli remain localized for the most part, and the general symptoms are due to toxin produced locally. Sloughing and fibrinous exudation take place locally at the seat of disease. Fatty degeneration of the heart, liver, etc., occur, and paralysis of the limbs and trunk muscles appear at a later stage.

The identity of the disease in man and animals is further shown by the curative action of antitoxin in both.

Although, therefore, in all probability the toxin produced by different strains is harmful to man in direct proportion to its toxicity for guinea-pigs, still it may perhaps be the case that the bacilli themselves in many instances find a better nidus for growth, or produce more toxin in one species of animal than in another, or in man.

The degree of pathogenicity of a given strain, therefore, may not be the same for the guinea-pig and man, but the existence of pathogenicity for the one may be taken as proof of ability to produce disease in the other.

Hofmann's Bacillus.

From the point of view of diagnosis, the relative importance of the various diphtheroids depends on the frequency of their occurrence and the ease or difficulty with which they can be distinguished from the true *B. diphtheriae.*

The diphtheroid which occurs with the greatest frequency in the human throat and nose, especially in catarrhal conditions, is that described by Hofmann in 1887, and generally known as "Hofmann's bacillus."

It is usually readily distinguished from the *B. diphtheriae* by its morphology. In films from young serum cultures stained by methylene blue it appears as a diplobacillus without any segmentation, except for one clear, unstained line across the middle, dividing it into two equal parts. It is shorter than *B. diphtheriae,* broader in proportion to its length, and usually slightly tapering from the central division towards the ends. Occasionally segmented forms occur. One of the chief characteristics is the uniform size and appearance of the bacilli seen in the film. When stained by Neisser's stain, polar granules are usually absent, but may occur, and are then generally of a smaller size than in *B. diphtheriae.*

Hofmann's bacillus is further distinguished by producing an excess of alkali in media containing glucose, and affording no evidence that acid is produced from glucose. The colonies on agar are larger, and more raised and opaque than those of *B. diphtheriae.*

The term "pseudodiphtheria bacillus" is often used as a synonym for *B. hofmanni*, but it has been employed in other senses by some writers, and should therefore be discarded. It was formerly much contested whether the bacillus of Hofmann was merely a variety of *B. diphtheriae* or a distinct organism.

In America, England, and Germany, however, it is now generally held that the two bacilli are quite distinct, and that though the bacillus of Hofmann belongs to the same group of bacteria as the *B. diphtheriae*, it has no relation to diphtheria.

In France Hofmann's bacillus (*Bacille pseudodiphtérique*) is regarded by many writers as a degenerate form of *B. diphtheriae,* which is liable to regain its virulence under favourable circumstances, and is then capable of causing true diphtheria (Sacquépée, 1910).

Park and Beebe (1894), by an extensive series of observations and experiments, showed that Hofmann's bacillus occurred frequently (9 per cent.) in healthy or catarrhal states of the throat and nose of persons who had not been in contact with diphtheria, at the same time pointing out that this bacillus was distinguished from *B. diphtheriae* by not producing acid in glucose culture media. It appears to be of much more frequent occurrence in some localities than in others.

Cobbett (Graham-Smith, 1904), examined 1724 children who had been in contact with diphtheria, and found Hofmann's bacillus in 39 per cent. in the throat. Of 10,570 healthy persons, records of whose examination were collected by Graham-Smith (1908*d*), 18·2 per cent. yielded Hofmann's bacillus from the throat.

Graham-Smith (1908*e*) discusses at length the relation of the *B. diphtheriae* to the bacillus of Hofmann, and comes to the conclusion, after consideration of the large amount of material at his disposal, that diphtheria and Hofmann's bacillus are not related to one another.

Out of numerous observations recorded by this author may be mentioned those made during an extensive epidemic at Cambridge (Graham-Smith, 1904). He found that the proportion of persons infected with Hofmann's bacillus was nearly the same amongst diphtheria convalescents, contacts infected with the *B. diphtheriae,* non-infected contacts, and non-contacts.

The writer (Arkwright, 1908) found in a school epidemic that of 537 boys examined, 118 (21 per cent.) harboured *B. diphtheriae,* and 182 (43 per cent.) of the 419 boys in whom the *B. diphtheriae* was not found yielded Hofmann's bacillus.

Besides the lack of epidemiological relationship between the *B. diphtheriae* and Hofmann's bacillus, there is a large amount of negative evidence derived from unsuccessful attempts to transform the one bacillus into the other by animal passage or artificial culture. The two or three occasions on which the transmutation is reported to have taken place have been isolated and unconfirmed.

Clark (1910) made an elaborate series of experiments with a view to altering the character of Hofmann's bacillus without success, and many other workers have failed in similar attempts.

Goodman (1908) claims to have increased the power of Hofmann's bacillus to produce acid from glucose, and to have diminished that of *B. diphtheriae* until these characters no longer afforded a means of distinguishing between them. The method which he adopted was one which depended on the selection from a large series of cultures, of those tubes only which showed the extreme degrees of acidity, and the repetition of this selection in a number of successive subcultures.

The one character (acidity) was altered by this method, but the other characters of the cultures were not shown to have been changed. Even if his experiments can be repeated, the change of a single character by selection directed to that one object is scarcely comparable to a natural mutation.

Diphtheroid Bacilli other than Hofmann's Bacillus.

It is impossible in this work to enter fully into the means of differentiation and the classification of the diphtheroid bacilli, a subject which has at present been very insufficiently worked out. The reader is, however, referred for information on the subject to Nuttall and Graham-Smith's book on the "Bacteriology of Diphtheria" (1908*f*).

Xerosis Bacilli.

The name of *B. xerosis* is used here for strains belonging to the group of diphtheroid bacilli which form acid from cane-sugar as well as from glucose. This classification is that used by Knapp (1904), Eyre and Flashman (1905), but their use of the name *B. xerosis* is not universally recognized.

None of the bacilli of this group are common inhabitants of the throat and nose, but one or other variety occurs fairly frequently in discharges from the ear due to otitis media, and in the urethra.

The bacillus to which the name is perhaps most frequently applied (Graham-Smith, 1908*g*) forms very small colonies on culture media, and grows very feebly in nutrient broth. The individual bacilli are very small, and usually cohere in masses.

Some of the diphtheroid bacilli which ferment cane-sugar form a thick whitish or yellowish creamy growth on agar, and may show large segmented forms on films. These latter strains are sometimes mistaken for *B. diphtheriae* in films from young serum cultures. The *B. septus*, which is described by Benham (1906) as fermenting cane-sugar, must for that reason be mentioned here, though he apparently regards it as identical with *B. coryzae segmentosus*, to be mentioned in the next paragraph.

Various other Diphtheroid Bacilli.

The remaining group of diphtheroid bacilli, consisting of those which produce acid from glucose, but not from cane-sugar, affords examples comprising several varieties, which are liable to cause difficulty in diagnosis. They are devoid of specific virulence for guinea-pigs, though some strains have been described by Rüdiger (1903) and others which are fatal to guinea-pigs, but these animals are afforded no protection by diphtheria antitoxin.

The members of this group which are most important in the present connection are those included under the names *B. coryzae segmentosus* (Cautley), perhaps the *B. septus* (according to some writers), and the non-virulent diphtheria bacilli, including the *B. maculatus* of Graham-Smith. These latter are very probably of more than one kind.

The *B. coryzae segmentosus* appears in films from young serum cultures as a much segmented bacillus, and may show polar bodies by Neisser's stain.

It may closely resemble some forms of *B. diphtheriae*, but is usually rather broader and more regular in size and shape, and is more evenly banded. The colonies on serum or serum agar are extremely small, and the growth in broth is very scanty, and is described as "stringy." On glucose media, acid is produced very slowly. The *B. coryzae segmentosus* is found much more frequently in the nose than in the throat, and occurs mainly during the acute stage of some varieties of catarrh. It has no pathogenicity for guinea-pigs.

*Non-virulent Diphtheria Bacilli.**

The group of non-virulent *B. diphtheriae* is made up of those strains which have no specific virulence for guinea-pigs, but otherwise are indistinguishable from one or other variety of virulent *B. diphtheriae*. Non-virulent *B. diphtheriae*, as a rule, are quite harmless for guinea-pigs, or at most produce little more than a small local swelling, which subsides without causing sloughing or loss of hair or illness of the animal, even when as large a dose as 2·5 c.c. is given. Even 5 c.c. or 10 c.c. may often be given subcutaneously without any general or severe local disturbance.

Graham-Smith has described one form of non-virulent *B. diphtheriae* as *B. maculatus*, which closely resembles morphologically a variety of virulent *B. diphtheriae*.

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* Kolmer (1912) has recently reinvestigated the relation of the morphological types of *B. diphtheriae* to virulence in 253 strains from cases of diphtheria. He considers solid and barred forms as only doubtfully *B. diphtheriae*. However, he does not appear to have tested the reactions with glucose and cane-sugar as a routine method, and consequently some of his solid and barred forms may have been identical with *B. hofmanni* and *B. xerosis* respectively.

The position of the non-virulent *B. diphtheriae* and their relationship to true virulent *B. diphtheriae* is at present undecided. As these bacilli have not infrequently been found present for a long time in persons suspected of acting as carriers, the question is one of considerable importance.

Non-virulent diphtheria bacilli are not of very common occurrence in the human throat.

Graham-Smith, from a large number of collected records, came to the conclusion that non-virulent *B. diphtheriae* occur in about 1 to 2 per cent. of the general population which has not been especially exposed to diphtheria, and he found these bacilli with the same frequency in persons suffering from diphtheria and in contacts.

From the above short account it will be seen that the differential diagnosis of the *B. diphtheriae* by its morphology is chiefly directed against the bacillus of Hofmann, and that certain other diphtheroids (some forms of *B. xerosis, B. coryzae segmentosus*) are much less easily excluded. Fortunately these latter bacilli only occur infrequently in the throat.

When the nose is examined the chance of error is greater, owing to the higher frequency with which certain diphtheroids occur here than in the fauces.

Material taken from cases of otorrhœa is far more liable to erroneous interpretation. Segmented diphtheroid organisms occur so frequently in the healthy and discharging auditory meatus that the morphological diagnosis of *B. diphtheriae* from this source can be made only with great reserve. It is therefore often necessary to isolate the strain of bacillus seen in the films before a definite opinion can be given on specimens from the ear.

III. OCCURRENCE OF THE BACILLUS DIPHTHERIAE.

PARTS OF THE HUMAN BODY IN WHICH THE B. DIPHTHERIAE IS FOUND.

In seeking for carriers of the diphtheria bacillus, a search must often be made in other situations besides the mouth. In some cases the saliva contains many *B. diphtheriae*, but as a rule the bacilli are most readily obtained by rubbing the sterile swab on the tonsils and the back of the pharynx. It not uncommonly happens that the nasal fossæ readily yield cultures of *B. diphtheriae*, but the results of nasal examinations are rather less reliable because of the frequency with which diphtheroids occur in that region. Of the latter perhaps the *B. coryzae segmentosus* is the most likely to cause confusion.

Membranous rhinitis may be very chronic, and has been shown to be associated for months with *B. diphtheriae*.

The examination of large numbers of persons, however, who have been in contact with cases of diphtheria shows that the *B. diphtheriae* is present more frequently in the throat than in the nose.

Virulent *B. diphtheriae* has occasionally been isolated from the ear discharge in cases of otitis media, but reports of the *B. diphtheriae* having been found in ear discharge and diagnosed by its morphology alone are of comparatively little value. Other bacilli belonging to the group of diphtheroids very frequently occur in this situation, and may so closely resemble *B. diphtheriae* that a satisfactory decision can be arrived at only after isolation of the bacilli.

Chronic laryngitis, as shown by a husky voice, may also occur in association with the *B. diphtheriae*.

Besides these more commonly recognized sites for the *B. diphtheriae*, the conjunctiva or the vaginal mucous membrane may occasionally be infected, but cases are not recorded in which the *B. diphtheriae* has persisted in these situations after the signs of disease have disappeared.

The skin is more frequently infected with *B. diphtheriae*, and infection may persist for a considerable length of time. It not infrequently happens in faucial diphtheria that a crack at the corner of the mouth becomes infected with *B. diphtheriae*, and then either becomes covered with membrane or secretes a serous discharge. The angles of the external nares may be similarly affected when there is diphtheria of the nasal fossæ.

When any sores are present on the face—*e.g.*, excoriated herpetic vesicles or those resulting from eczema—it may happen that the breaches in the surface epithelium give entrance to *B. diphtheriae*, which lives on the surface of the ulcer without causing much reaction in the tissues or definite membrane formation.

In this way ulcers and broken vesicles or fissures of the skin in various parts of the body may be attacked, and may remain infected when the *B. diphtheriae* can no longer be found in the throat or nose.

A case of this kind is reported by Porter (1912). The patient was a woman, one of whose children had recently suffered from faucial diphtheria. The order in which the two infections occurred was not quite clear. The mother had suffered for some time from chronic eczema of the neck, forearms, and hands. Pustules infected with *B. diphtheriae* appeared on the wrists. The bacillus, isolated by the writer from one wrist and from the neck, proved to be virulent *B. diphtheriae.* The nose and throat swabs taken on at least four occasions gave negative results.

Whilst the skin was infected, she paid a visit of half an hour's duration to an isolated cottage. Four or five days later two children from this cottage sickened with diphtheria.

The skin lesions cleared up with local treatment, and without the administration of antitoxin. In this instance a "skin-carrier" appears almost certainly to have caused diphtheria in two children.

Cases of skin infection with the *B. diphtheriae* have been recorded in which a skin disease resembling eczema has been held to be due entirely to this micro-organism. This view appears to have been confirmed by rapid improvement after a single dose of antitoxin; in other cases repeated injections of antitoxin have been required in order to produce any amelioration. The bacteriology, however, of these cases has not been very thoroughly investigated. Ten cases of eczema, impetigo, herpetiform dermatitis, from which *B. diphtheriae* were isolated, are narrated by G. W. Dawson (1910), who personally saw four of the cases. Four of the ten cases got well whilst under treatment with diphtheria antitoxin.

In one case animal experiments were performed, and the strain of *B. diphtheriae* was shown to be pathogenic.

The association of impetiginous eczema of the head and face with conjunctivitis is said to be usual in these cases.

Cuno (1902) mentions a case of extensive eczema of the face and head, from which virulent *B. diphtheriae* was isolated, and which quickly got well after injection of antitoxin.

Cases of whitlow in diphtheria convalescents, in which the local lesion on the finger is infected with *B. diphtheriae,* have been recorded by several writers.

Probably most cases of "skin diphtheria" are due to secondary infections with the *B. diphtheriae* from the throat or nose engrafted on some pre-existing vesicular eruption or fissures of the skin.

Non-pathogenic diphtheroid bacilli are commonly found on the skin, and their occurrence renders necessary a very complete examination of a bacillus from the skin, before its identity with the *B. diphtheriae* can be considered to be established.*

THE OCCURRENCE OF THE B. DIPHTHERIAE IN CASES OF CLINICAL DIPHTHERIA, IN CONTACTS, IN THE GENERAL POPULATION, AND ALSO IN THE LOWER ANIMALS, ETC.

Occurrence of B. Diphtheriae in Cases of the Disease.

In cases which have been clinically diagnosed as diphtheria the bacillus is found in from 67·5 to 82 per cent., according to different observers. Graham-Smith (1908), from collected records of examinations of 30,000 certified cases, found the average percentage of positive results was 71 per cent.

Scheller (1909) says that in swabs from about 30 per cent. of cases diagnosed clinically as diphtheria with exudate he could not find the *B. diphtheriae.* However, in almost all these cases in which the negative bacteriological result did not agree with the early clinical appearances, he heard later from the doctor that there was no further development of the case to support the initial diagnosis of diphtheria.

This percentage of positive results from bacteriological examination is as high as can be expected, considering the ease with which the *B. diphtheriae* may be overgrown in cultures, the early disappearance from the throat in some cases, and the probable occurrence of cases of sore throat which closely resemble those of diphtheria, but are really of a different nature.

Occurrence of the B. Diphtheriae in Convalescents.

In a large number of convalescents the bacillus is still present after the membrane or exudate has disappeared from the part attacked.

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* Conradi and Bierast (1912) have quite recently stated that in no less than 30 per cent. of cases of diphtheria they found the *B. diphtheriae* in the urine, and they suggest that such findings throw light on the origin of certain forms of cutaneous diphtheria, particularly in the region of the genital organs. The evidence, however, that the organisms found by them were genuine diphtheria bacilli is entirely insufficient.

The ability of such persons, for a certain length of time after apparent recovery, to communicate the disease to others, has been readily conceded by clinicians on the clinical ground of observed instances of infection, and on the analogy of other known infectious diseases.

The agency of convalescents in the spread of the disease has therefore generally been recognized apart from bacteriological examination.

The demonstration of the persistence of the bacillus in some convalescents makes it possible to say which convalescents are dangerous, and for how long they remain so.

As a rule, about half of those who have had diphtheria still retain the bacillus after the local membrane or exudate has disappeared; and, further, about 25 per cent. are still infectious after another seven to ten days.

These persons may be called "convalescent carriers."

Presence of the B. Diphtheriae in Contacts.

On the other hand, a search for the bacillus amongst those in direct association with the patient reveals the fact that a considerable number of individuals in his immediate surroundings are invaded by the bacillus without showing any signs of disease. These "contact carriers" are generally known as "healthy carriers." The proportion of those persons in close contact with the disease who are found to harbour the bacillus in the throat or nose depends to some extent on the closeness of the contact and the age of those exposed in this way to infection.

For instance, where, as among the poorer classes, numerous young children are living in few rooms, and when isolation is not practised, the proportion of contacts infected is very high. If the contacts in such a family are frequently examined, it may be found that every member of the household harbours the bacillus for a longer or shorter period.

The age of the contacts appears to have some effect on the occurrence of carriers. Children under five years or over eight years are more likely to contract acute diphtheria, but are less likely to become carriers than children between five years and eight years, according to the observations of Thomas (1904).

Scheller (1906) expresses the opinion that as a rule all the members of a family in which diphtheria breaks out sooner or later become infected if they come in contact with the patient. He cites the instance of a school-teacher's family in which seven of the eight members became carriers in the course of about six weeks.

MEMBERS OF FAMILY OF SCHOOL-TEACHER EXAMINED REPEATEDLY BY SCHELLER.

Sex.	Age.	Healthy or Diphtheria.	June 10	June 30	July 9	July 15	July 22	July 29	Aug. 5
Female ..	7 years	Diphtheria, recovered June 8	+	+	+	0	+	0	0
Female ..	$2\frac{3}{4}$,,	Healthy	0	0	0	+	0	0	0
Female ..	9 ,,	,,	+	0	+	+	+	0	0
Male ..	8 ,,	,,	+	+	+	+	0	+	0
Male ..	$1\frac{1}{2}$,,	,,	0	0	0	0	0	0	0
Teacher ..	39 ,,	,,	+	+	+	0	0	0	0
Wife ..	31 ,,	,,	+	0	+	+	0	0	0
Female servant ..	17 ,,	,,	0	0	+	0	0	+	0

All the members of the family except one were invaded.

From amongst the very numerous records the following instances may be selected to illustrate the occurrence of carriers amongst contacts:

Aaser (1905), among 89 healthy men in a cavalry regiment, found 17 (19 per cent.) carriers, all of whom were invaded by virulent strains.

Peck (1895) examined 100 scholars in a boarding-school, and found that 31 per cent. of them were carriers.

Kober (1899), in Breslau, examined 128 persons who had been in contact with cases of diphtheria, and found that 15 (11 per cent.) yielded the *B. diphtheriae.* Of these 15, however, 5 had mild sore throats. It was found that of 139 "contacts" who had slight sore throats, 97 (70 per cent.) yielded *B. diphtheriae;* whereas of 223 normal contacts, only 10 (8 per cent.) gave positive results, so that these cases of sore throat were no doubt mild cases of diphtheria.

During an epidemic Cobbett (1901) examined 650 adults and children, and found 19 (3 per cent.) carriers.

The Minnesota State Board of Health (1899, 1900) reports that in five schools containing 225 children the total number of carriers discovered was 30 (13 per cent.), and that the number of carriers in the individual schools varied from 3 to 25 per cent.

Graham-Smith (1902), during an epidemic of diphtheria, examined 519 persons in schools, and found 54 (10·4 per cent.) who harboured *B. diphtheriae.*

The same writer in 1904 (Graham-Smith, 1908*h*) examined 1,094 persons, including 29 notified cases of diphtheria, at Cambridge during an epidemic. He found 33 healthy carriers harbouring virulent *B. diphtheriae.* About half the persons, therefore, who were infected with virulent *B. diphtheriae* were cases of diphtheria, and the other half were healthy carriers. The following are further examples illustrating the proportion of carriers found amongst contacts during the epidemic occurrence of diphtheria.

Ustvedt (1906), in Christiania, from May 28 to June 20, 1903, examined 967 children in public schools, and found 9·2 per cent. who harboured the *B. diphtheriae.* This was in the epidemic season for diphtheria, 251 cases having occurred during June, 1903. In September of the same year, out of 4,277 children examined, 191 (4·5 per cent.) yielded the *B. diphtheriae* as diagnosed morphologically.

Circumstances affecting the Number of Carriers.

Thomas (1904), basing his conclusions mainly on a large experience in London schools, divides carriers in infected schools into four classes :

1. Actual mild cases of diphtheria, comprising 80 per cent. of all the carriers.
2. Children from infected houses who presented no symptoms (12 per cent.).
3. Cases of recrudescence after notified diphtheria (6 per cent.).
4. Cases with no symptoms nor demonstrable contact with cases of diphtheria (2 per cent.).

He found that of the carriers detected in schools, 85 per cent. were between five and eight years old.

In London the heaviest incidence of the disease falls on children of three to five years of age. There is then a marked decline in the incidence between the fifth and eighth years.

The carriers are therefore most numerous at an age when actual cases of diphtheria are less frequent, and the decreased susceptibility to diphtheria is apparently associated with an increased tendency to harbour the bacillus without the production of signs of disease.

Thomas as a rule confined his bacteriological examination of the school classes to those who presented obvious general or local signs of ill-health, such as pallor or nasal discharge.

He and many other observers are also of opinion that in this way the important carriers in a school class may usually be detected without making a bacteriological examination of every member of the class. This, however, is certainly not always possible.

An instance of a school in which a very high percentage of carriers was found is reported by Seydell (1909). At his first examination of the pupils, he found that 72 per cent. were carriers. A week later 22 per cent. yielded the *B. diphtheriae*, and eleven days later (*i.e.*, eighteen days from the first examination) no carriers were found. The majority of the carriers had large tonsils.

Graham-Smith (1908*k*) gives the percentages of carriers found among healthy contacts in different classes of the community.

He derives his figures from statistics collected from various sources, including over 9,000 examinations :

Persons attending on the sick ..	37 per cent.	(12 to 48 per cent.).
Relatives of the sick	29 ,,	(11·7 ,, 40 ,,).
Hospital wards and institutions ..	14 ,,	
Schools	8·7 ,,	(2·5 ,, 45 ,,).
Other contacts	36 ,,	
Infected by milk and contact ..	32 ,,	

The percentage of carriers on the whole was about 14 per cent. The percentage of carriers, however, varies very much for each class, and probably the circumstances and peculiarity of each outbreak are of great importance in determining the number of carriers that occur.

Near relations, attendants on the sick, and young children in some school outbreaks, are those which yield the highest percentage of carriers.

Some interesting details of outbreaks occurring in institutions for children in Berlin have recently been published by Seligmann (1911). They show great variations in the proportion of carriers.

1. In one school class with 46 children, 33 yielded *B. diphtheriae.*

2. In another school 8 cases of sore throat (in 4 of which *B. diphtheriae* were found) had occurred in five weeks. The school was closed for a fortnight. On reassembling, of 51 children, 9 (18 per cent.) were carriers.

3. Another school was closed for one week. Four cases of diphtheria occurred whilst the school was closed, and 3 after reopening. Of 31 persons (teachers and scholars), 5 were carriers.

4. In another school three classes were involved in an epidemic of diphtheria, but only one healthy carrier was found. In this case probably, the disease was spread by infection in the home.

5. In a boarding institution for children 10 cases of diphtheria occurred in twelve days. The first case was one of mild sore throat. Among the inmates — 47 persons in all were examined—3 carriers were found, but only one of these was a healthy carrier, while 2 were suffering from mild attacks of diphtheria. Therefore in this case probably all who received the infection, except one, were attacked by the disease.

Diphtheria was in all likelihood introduced into this institution by a boy on February 27. The first case did not occur till March 15. Therefore the infection remained in the school for over a fortnight before the first clinical case of diphtheria occurred. On March 27, after the lapse of a month, when the bacteriological examination of the school was made, only one healthy carrier was to be found.

6. Diphtheria broke out in an orphanage on June 27, when three cases occurred, and on June 29 two more cases of sore throat were reported. All the inmates accordingly were examined bacteriologically on three occasions.

On July 3 84 persons were examined, and 2 healthy carriers were found. After the second examination another case of diphtheria occurred in a child who had previously given a negative result. At the third examination 2 new carriers were found, and a mistress who had recently arrived was found to be infected.

The source of infection was probably a child with nasal discharge, who came to the orphanage on June 8 from a home where his brother had recently had diphtheria.

This carrier, then, must have remained a long time (from June 8 to 27) in the orphanage without causing any cases of diphtheria.

7. In an institution for idiots there had been several cases of diphtheria, one of which was severe, between December 10, 1909, and March, 1910. In May, 1910, 126 persons were examined and 13 carriers found, one of whom was a nurse.

As a result of this examination, with the consequent isolation of carriers, only one case of diphtheria occurred from June, 1910, to March, 1911.

8. In a children's home in which diphtheria was prevalent

27 nurses were employed, and 10 of these proved to be carriers.

The proportion of carriers amongst the healthy members of communities in which diphtheria has broken out varies widely even when, at first sight, circumstances appear to be very much alike. Seligmann, however, points to a general parallelism between the number of cases and the number of carriers in the different wards of an institution for poor children. He examined the different wards bacteriologically, with results which appear in the table.

The proportion of carriers to cases of disease depends, however, also on the care with which cases of mild sore throat are sought out.

Occurrence of Cases of Diphtheria compared with Number of "Healthy Carriers" detected.

Ward II.	1 case of diphtheria	1 carrier.	
,, I.	2 cases ,,	4 carriers.	
,, IV.	4 ,, ,,	6 ,,	out of 24 persons.
,, III.	4 ,, ,,	10 ,,	,, 23 ,,
,, V.	8 ,, ,,	18 ,,	,, 35 ,,

In one ward for infants which contained 53 children and 6 nurses at the first two examinations—*i.e.*, during the first fortnight—only one carrier was found.

Eighteen days from the first examination suddenly 7 more carriers were detected, and these were probably infected by a wet-nurse who had concealed a mild attack of sore throat.

In Ward III. 4 cases of diphtheria had occurred during the last three months. The ward contained 19 children and 4 women—23 persons in all—and 10 carriers were found, including a maidservant. None of the carriers had recently recovered from diphtheria.

In Ward IV. there had been 4 cases of diphtheria in the last three months. There were 18 children and 5 nurses, and one maidservant in this ward. Six carriers were found, of whom one had recently had an attack of diphtheria.

In Ward V. 8 cases of diphtheria had occurred in the last five months. The children and nurses together numbered 35. During the examination 2 more cases of diphtheria were discovered. Eighteen carriers, including 5 nurses, were found, and 2 of these had recently had diphtheria.

The result of these examinations and the isolation of those infected was that from January 1 to May 27 only two cases occurred in all five wards, and both were cases newly admitted, and not examined for *B. diphtheriae* on admission.

During the same time 45 cases of diphtheria occurred in the rest of the infirmary.

The source of infection was generally traced to children who had recovered and had returned too soon from isolation, or to very slight cases of illness which had been overlooked.

Of 46 carriers, 8 were either nurses or maidservants.

The number of cases and of healthy carriers (contacts) which occur in some epidemics appears to be about equal. In an epidemic which occurred at Crewe, and was recorded by Macdonald (1911), the following results were obtained during the six months of prevalence of the disease. The carriers who were detected were only 90, as compared with 157 certified cases. The first column in the annexed table shows the number of persons found positive who were notified; the other columns show the carrier cases found on examining those in contact with the notified persons.

Month.	Notified Cases.	Contact Carriers.		
		Home.	School.	Total.
March	49	13	7	20
April	31	15	3	18
May	25	10	3	13
June	27	11	10	21
July	15	10	5	15
August	10	3	0	3
	157	62	28	90

This epidemic does not appear to have been due in the main to school influence.

Although the *B. diphtheriae* occurs very frequently in the healthy who are in contact with diseased persons, still, amongst the inhabitants of large towns who are not known to have been associated with the disease the number of those in whom the bacillus can be found forms only a very small percentage of the whole population. In country places where diphtheria has not occurred for a long time the *B. diphtheriae* may be completely absent.

Some of the earlier records of bacteriological examinations are vitiated by the confusion of the *B. diphtheriae* and Hofmann's bacillus. Even at the present day many French writers refuse to admit that a sharp distinction exists between the two bacilli except as regards virulence.

In following the accounts of a bacteriological investigation of an outbreak of diphtheria, it is therefore important to note the thoroughness with which the examination of the strains has been conducted, and the tests which have been used in order to identify them.

Attention should be specially directed to the standard of morphology which is accepted by the observer, and whether the tests for the production of acid from glucose and for virulence have been employed.

The locality in the body from which the bacillus has been derived is also of some importance (*vide* p. 178).

OCCURRENCE OF THE B. DIPHTHERIAE IN APPARENTLY HEALTHY PERSONS AMONGST THE GENERAL POPULATION.

Since those in contact with diphtheria patients so frequently become carriers of *B. diphtheriae*, and apparently are capable of passing it on to others, it is to be expected that, in communities in which diphtheria is endemic, a certain number of persons not known to have been in contact with a case of diphtheria will be found to harbour the *B. diphtheriae* on search being made.

This is the case especially among school-children, no doubt on account of their age predisposing them to mild infection with the *B. diphtheriae*, and also because they are so closely congregated together for lessons and play.

The proportion of healthy children who have not been in contact with known cases of diphtheria, but who harbour the bacillus, varies very much in different places, at different seasons, and in different years.

Large numbers of such school-children have been examined, and the observations afford statistics from which a general estimate of the prevalence of carriers in this class of persons may be formed.

As was pointed out by Loeffler, if the history and surroundings of persons not known to have been in contact with diphtheria, but who are found to harbour *B. diphtheriae*, are carefully inquired into, it frequently happens that either they have themselves recently suffered from an attack of sore throat, or they have been in contact with a case of diphtheria.

Graham-Smith (1908*l*), from collected records of 2,132 carefully-made observations, gives 0·18 per cent. as the average proportion of persons who have not recently been in contact with diphtheria cases, but who are found to be carriers of virulent *B. diphtheriae.* Non-virulent diphtheria bacilli, he concludes, are present in about 2·62 per cent., making a total percentage of 2·8 per cent. of carriers of virulent and non-virulent bacilli amongst persons belonging to this category.

Amongst 4,729 persons (Graham-Smith, 1908*m*) examined, who were believed not to be contacts, but whose circumstances were less carefully inquired into, 4·3 per cent. yielded bacilli morphologically, resembling *B. diphtheriae* in every respect.

When diphtheria is not known to have occurred in a community for some time, a complete absence of carriers may be found on making an examination.

Thus, Cobbett in 1901 (Graham-Smith, 1908), in an uninfected school in Cambridge, found no *B. diphtheriae* amongst 43 children.

Graham-Smith (1903) examined 362 healthy non-contacts, and found *B. diphtheriae* in only one person. This strain, when isolated, proved to be non-virulent.

Ustvedt (1906) found in a country school near Christiania, in which no diphtheria had occurred for eight years, that none of the 86 children in the school yielded *B. diphtheriae.* In another school of 53 children, where 4 cases of diphtheria had occurred four to five months before, no *B. diphtheriae* could be found.

Büsing (1907) examined 245 children and 77 adults in Bremen. He found no carriers of virulent *B. diphtheriae,* but his figures for carriers of non-virulent *B. diphtheriae* were unusually large. He states that there had been only a few cases of diphtheria.

Of the 322 persons examined, though none were carriers of virulent *B. diphtheriae,* 49 yielded non-virulent *B. diphtheriae.*

Kober (1899) examined 600 healthy school-children, who were not known to have been in contact with cases of the disease. He found that 15 yielded *B. diphtheriae—i.e.,* 2·5 per cent.

Of these, 10 on inquiry were found to have had some connection with cases of diphtheria. Therefore 5 carriers occurred among "non-contacts"—*i.e.*, 0·85 per cent.

Park and Beebe (1894), in New York, examined the throats of 330 normal children. They found that 32 (9·7 per cent.) yielded *B. diphtheriae.* Of these 32 strains, 8 were virulent (2·4 per cent.) and 24 were non-virulent (7·5 per cent.). Von Sholly (1905) found in 230 normal children in New York that 12 (5·2 per cent.) yielded *B. diphtheriae*, 3 of the strains being virulent, and 9 non-virulent, while 61 children (or 26·5 per cent.) yielded Hofmann's bacillus.

M. E. Pennington (1907), in Philadelphia, examined 375 apparently healthy school-children, 40 of whom (9·3 per cent.) were found to be harbouring the *B. diphtheriae;* and of the strains isolated only 14 per cent. were fully virulent, and 30 per cent. of modified virulence. These figures, as regards virulence, are contrasted with those showing the virulence of strains isolated from 25 diphtheria convalescents; of these latter 22 were virulent and 2 non-virulent; whereas the strain from one patient was at first virulent, and later non-virulent. The virulence was tested by injecting the growth from a culture on solid serum into a guinea-pig.

Von Sholly (1907) examined the throats of 1,000 children in tenement houses who appeared to be healthy, and who were not known to have been in contact with diphtheria. Eighteen of these yielded virulent *B. diphtheriae* (1·8 per cent.).

Fifty children had the throat and nose examined, and of those one had virulent *B. diphtheriae* in the nose only. It was noted that Hofmann's bacillus occurred twice as often in the nose as in the throat.

Two hundred and two "family contacts"—*i.e.*, persons in whose family a case of diphtheria had recently occurred—were examined; 20 (10 per cent.) yielded the *B. diphtheriae.* Of these strains, 14 (7 per cent.) were virulent, and 6 (3 per cent.) non-virulent.

DIPHTHERIA CARRIERS AND SCARLET FEVER.

Extensive examinations have been made of patients admitted to scarlet fever hospitals, on account of the importance of diphtheria as a complication of scarlet fever.

Pugh (1902) made cultures from the fauces of 415 cases not clinically suggesting diphtheria admitted to the scarlatina ward of a fever hospital. He found that 17 were harbouring the *B. diphtheriae*, and of these 5 strains were non-virulent, and the remainder were not examined for virulence.

He also examined the throat and nose of 414 patients in the hospital, who presented no clinical evidence of diphtheria. Of these, 33 (7·9 per cent.) yielded *B. diphtheriae* (6 non-virulent). The strains which were tested for virulence in both series were shown to produce acid from glucose.

In 10 of the 33 carriers the *B. diphtheriae* was found in both the nose and the fauces (3 non-virulent), and in 22 in the nose only (3 non-virulent).

Cumpston (1907) examined the throats of 1,017 cases admitted to hospital as scarlet fever patients. He found *B. diphtheriae* in 29 (5·8 per cent.); and out of 165 patients whose noses he examined, he found *B. diphtheriae* in 21 (12·7 per cent.).

Porter (1912) found that scarlet fever convalescents were frequently infected with *B. diphtheriae*, which persisted after their return home, and caused outbreaks of diphtheria. He examined 29 patients in a scarlet fever ward, and found 5 infected with *B. diphtheriae*; and of 41 scarlet fever convalescents recently discharged, 10 were carriers of the bacillus.

The virulence of the strains of *B. diphtheriae* isolated from scarlet fever cases by Cumpston and Porter is not recorded.

"Precocious Carriers."

By a "precocious carrier" is meant a person in whom the *B. diphtheriae* is found for a longer or shorter time without any symptom of disease appearing, but who eventually develops diphtheria.

Thus Wesbrook (1898) mentions a case in which *B. diphtheriae* was present two months before the onset of the disease.

Kober (1899) records a case of a healthy person with no sign of disease in the throat, although *B. diphtheriae* was present, who six days after examination developed diphtheria. Scheller (1906) says he has found *B. diphtheriae* in the fauces four weeks before an attack of diphtheria. He also gives an account of a healthy carrier in whose nose alone the *B. diphtheriae* was found before operation on the nose. Two days after the examination she had a typical attack of diphtheria in the tonsils, although the wound healed naturally.

Similar cases of post-operative diphtheria occurring in carriers have frequently occurred.

" Contacts " or " Abortive Cases "

Many of the carriers found during outbreaks of diphtheria in families and schools are really mild cases of diphtheria which have escaped notice altogether, or which have been passed over as cases of mild sore throat or nasal catarrh.

Such carriers should strictly be classed with convalescents, rather than as " healthy carriers," but the distinction is frequently quite impossible in practice.

When a search is made in a community for carriers, it is especially important to examine any person suffering from slight sore throat or nasal discharge. Most carriers have such clinical signs, but not all. Nasal carriers are perhaps of special importance, and some writers lay special stress on their frequency and dangerous character.

It is not always clear why some epidemics are marked by the discovery of few carriers in proportion to the number of cases, and others by the opposite relation of the numbers.

The following factors have a controlling influence in some outbreaks :

1. As shown by Thomas, the age of the persons forming the community in which the outbreak occurs is of great importance. Children of five to eight years are much more likely to become " healthy carriers " than definite clinical cases of diphtheria.

2. The general health of the individual who becomes infected may determine whether he develops into a definite case of diphtheria, or merely harbours the *B. diphtheriae* whilst remaining in fair health. Seligmann points this out with regard to whooping cough and influenza. The occurrence of either of these complaints in a ward immediately increased the number of cases of diphtheria.

3. An unhealthy state of the naso-pharynx probably has a considerable effect in favouring the retention of the *B. diphtheriae*, as many carriers have enlarged tonsils or adenoids.

4. Whether the degree of virulence or some such quality of the strain of bacillus has any effect on the frequency with which

those infected develop clinical diphtheria is very doubtful. At any rate highly virulent bacilli are frequently isolated from healthy carriers.

5. The care and persistence with which mild cases of sore throat or nasal diphtheria are sought for, has no doubt a considerable influence on the relative numbers of persons set down as " carriers " or " cases of disease."

SIGNIFICANCE OF NON-VIRULENT STRAINS OF B. DIPHTHERIAE.

The question as to how much significance must be attached to the occurrence of the non-virulent strains of the *B. diphtheriae* is of considerable importance, and is best considered as a whole in this section, since much of the evidence for or against the acceptance of the non-virulent strains as true *B. diphtheriae* rests on the frequency of their occurrence in cases of clinical diphtheria, convalescents, contacts, healthy non-contacts, etc.

At first sight it may seem natural to suppose that non-virulent strains are merely strains which have lost their virulence, as happens with many other pathogenic bacteria in artificial culture or as the result of passage through insusceptible animals. However, in the case of the *B. diphtheriae*, the character usually called " virulence " appears to be of a different, perhaps more complex, kind than in the case of bacteria like *B. anthracis* or the pneumococcus. In the case of *B. diphtheriae* the so-called " virulence " or pathogenicity, as usually tested by injecting a guinea-pig with a forty-eight hours' broth culture, is dependent on the amount of toxin which has been excreted into the culture medium, and the behaviour of the bacillus in the animal body. This latter character again depends on (1) the ability of the bacillus to thrive in the body, and (2) the activity with which it excretes toxin in the tissues.

The ability to thrive in the animal body may possibly diminish after artificial culture, but the toxigenic power appears to increase when the bacillus is grown on artificial media.

This dissimilarity between the property called " virulence " in the case of *B. diphtheriae*, and of many other pathogenic organisms, increases the difficulty of testing this property. It also renders an argument as to the probability of the *B. diph-*

theriae regaining virulence by passage or culture very untrustworthy if based on analogy with other kinds of bacteria.

In favour of the view that non-virulent strains of *B. diphtheriae* are to be regarded as the true *B. diphtheriae* which have lost their virulence and may presumably regain it at some future date are the following considerations :

1. The " resemblance " in microscopical appearance and cultural characters of non-virulent strains with some types of virulent strains.

2. The great variability of true strains of *B. diphtheriae*, which are known to be virulent. This variability is expressed in the microscopical morphology, the appearance of the colonies, and the rate of growth on artificial media. Variations in the toxigenicity and virulence for guinea-pigs also occur (Arkwright, 1911), though this has been questioned by some writers.

3. The absence of non-virulent as well as virulent strains from some communities in which diphtheria has not occurred for a long time.

4. The occasional occurrence of non-virulent strains of *B. diphtheriae* in cases of clinical diphtheria and during convalescence, and the high proportion of such non-virulent strains found in " contacts " in some epidemics.

5. Instances have been recorded of the existence of a high antitoxin content in the serum of persons who have recently suffered from diphtheria and sore throat accompanied by non-virulent *B. diphtheriae*.

6. The production of a decided increase of antitoxin in the blood serum of a horse after inoculation with filtrates from cultures of non-virulent *B. diphtheriae* (Arkwright, 1910).

Absence of Non-Virulent B. Diphtheriae in Communities free from Diphtheria.

That non-virulent *B. diphtheriae* are not universally present, even in the absence of diphtheria from the community, is shown by the observations of Ustvedt (1906). He records the results of examinations of two schools in which no diphtheria had occurred recently, and in which no *B. diphtheriae*, either virulent or non-virulent, were found (see also above, p. 183).

Cobbett (Graham-Smith, 1908*o*) found during an epidemic of diphtheria at Cambridge that in one school containing 43 children, in which there had been no cases of diphtheria, no carriers of *B. diphtheriae*, virulent or non-virulent, could be found. In a further careful examination of 90 healthy persons he found no *B. diphtheriae*, virulent or non-virulent.

OCCURRENCE OF NON-VIRULENT STRAINS OF B. DIPHTHERIAE IN CASES OF DIPHTHERIA AND "CONTACTS."

The proportion of non-virulent to virulent strains in diphtheria contacts appears to be high in some epidemics, and a fair number of cases of diphtheria and convalescents have been recorded in which only non-virulent *B. diphtheriae* has been found.

Cobbett (1901*a*) (Nuttall and Graham-Smith, p. 232) isolated nine cultures of *B. diphtheriae* from 19 infected "contacts." Six were virulent and 3 non-virulent.

Graham-Smith (1904) tested the virulence of the strains of *B. diphtheriae* isolated from 56 healthy persons who had come into contact with cases of diphtheria. Thirty-eight strains were fully virulent and 18 totally non-virulent.

Cobbett (1901*b*) found among 63 school-children (contacts) 13 who were carriers, and he tested the virulence of 10 of the strains. Six were virulent, and 4 non-virulent. This would appear to indicate that 12·3 per cent. of the children had virulent *B. diphtheriae* and 8·2 per cent. non-virulent *B. diphtheriae.*

Stadler (1909), amongst 464 healthy children in an institution in Zurich, in which a few cases of diphtheria had recently occurred, found that 18 yielded *B. diphtheriae* on examination. He isolated 17 of the strains, and found that 6 (one-third) were virulent and 11 non-virulent. This would imply that 1·3 per cent. of the children harboured virulent and 2·6 per cent. non-virulent *B. diphtheriae*, which is a very low percentage of carriers of virulent strains for an infected school, and a percentage of carriers of non-virulent strains about equal to that in the general population (Graham-Smith).

The present writer (Arkwright, 1908) found a high proportion of non-virulent *B. diphtheriae* among 20 strains which he isolated from the throat or nose of the boys in a school which he examined on account of an epidemic of diphtheria. The *B. diphtheriae* was obtained from 23 per cent. of the 591 boys. Of 20 strains isolated, 7 were completely non-virulent (*i.e.*, 35 per cent. of the isolated strains), and of the remainder 4 were fully virulent, whilst 9 were of lower virulence.

If the proportion of virulent to non-virulent was fairly represented in the 20 strains isolated, then 7 per cent. of all the boys were harbouring non-virulent *B. diphtheriae.*

Six of the seven non-virulent strains which were isolated came from boys who had not had sore throats recently. The seventh strain came from a boy who had a very bad sore throat two months before, and who had been the first case which clinically resembled diphtheria. At the time of examination, and intermittently since his illness, he had suffered from a purulent nasal discharge, and for this and other reasons was under suspicion as a means of spreading the disease. The non-virulent bacillus was isolated from his throat and nose on several occasions. In this case, therefore, the association of a completely non-virulent strain of *B. diphtheriae* with nasal discharge following severe diphtheria strongly suggests a connection between the disease and this non-virulent strain of bacillus.

Porter (1912) records an outbreak of diphtheria in the autumn of 1911 which he believed he had traced to two chronic nasal carriers who lived in neighbouring houses. One of the chronic carriers was a girl of thirteen who had regularly attended Sunday-school and a girls' club. She was in hospital in 1909 on account of chronic infection of the nose. Early in 1910 several swabs gave positive results.

The second carrier—a girl aged ten—was attending school. She had scarlet fever in March, 1909, and was found to have the *B. diphtheriae* in her nose on admission. In April, 1910, she yielded a negative result. No virulence tests were made till December, 1911, when the strains of *B. diphtheriae* isolated from both these chronic nasal carriers were examined by the present writer and found to be non-virulent.

Pennington (1907) found that of 25 diphtheria convalescents 22 yielded virulent *B. diphtheriae,* 2 non-virulent *B. diphtheriae,* while one of the patients yielded at first a virulent, and later a non-virulent, strain.

The present writer found both a virulent and a non-virulent strain at the same time in the throat of a child who was attending a school where diphtheria had been present some months previously. He also examined 24 convalescent cases at least six weeks after onset of the illness. They were in isolation in the diphtheria wards of two fever hospitals on account of the persistence of the *B. diphtheriae.* The writer found that the strains from 12 of these persons were quite non-virulent. From 12 others virulent types were recovered, and from one both virulent and non-virulent strains were obtained at the same time. Sixteen of these cases could be analyzed further, according to the definiteness of the attack of diphtheria, and the time which had elapsed since the onset. The cases which were returned as severe, moderately severe, and laryngeal may, for this purpose, be classed simply as severe and the remainder as mild types of diphtheria.

Of six non-virulent strains, four came from severe cases of diphtheria, and two from mild cases, with an average duration of twelve and a half weeks of isolation. Of ten virulent strains, eight came from severe cases of diphtheria and two from mild cases, with an average lapse of time since the onset of the disease of ten weeks. No great difference was therefore found between the carriers of virulent and non-virulent bacilli in these respects.

Amongst 30 clinical cases of diphtheria examined by Cobbett in one outbreak (1901*b*), 3 yielded only non-virulent strains of *B. diphtheriae*, and he also found non-virulent *B. diphtheriae* in the elder sisters of the patients. In this series non-virulent strains were recovered from 8 out of 18 contacts who remained well.

An interesting observation was made by Lubowski (1900), who records the presence of a high antitoxin content in the serum of a patient who had recently recovered from a sore throat associated with the non-virulent form of *B. diphtheriae.*

Too much stress must, however, not be laid on the comparatively small numbers of observations of this kind on record. The occurrence of non-virulent *B. diphtheriae* is sometimes fairly high amongst healthy persons, and in some instances in which non-virulent bacilli have occurred with unusual frequency in schools and hospitals, the non-virulent strains may possibly have been passed from one child to another as a secondary infection.

NON-VIRULENT B. DIPHTHERIAE IN NON-CONTACTS.

V. Sholly (1905) found in New York, on examining the throats of 230 apparently normal children, that 3 (1·2 per cent.) yielded virulent strains, and 9 (3·9 per cent.) non-virulent strains of *B. diphtheriae.* In addition 61 children yielded Hofmann's bacillus.

This result is compared by v. Sholly with a similar examination by Park and Beebe (1894), at a time when diphtheria was much more prevalent and more fatal. At that time 330 normal children were examined, and 8 (2·4 per cent.) found to harbour virulent strains, and 24 (7·3 per cent.) non-virulent strains of *B. diphtheriae.* Both varieties of *B. diphtheriae* were more frequent in the earlier examination, when diphtheria was more prevalent. The proportion of non-virulent *B. diphtheriae* is high, and the numerical relation of virulent to non-virulent (1 to 3) is curiously maintained.

Among 245 children examined at Bremen by Büsing (see p. 189) 40 carriers of non-virulent strains were found, and among 77 adults, 8 carriers of non-virulent *B. diphtheriae.* No virulent strains were recovered.

The percentage of non-virulent *B. diphtheriae* found by him is unusually large, but he may have overestimated the number of the non-virulent types, as he does not appear to have used the glucose test, and therefore his non-virulent class may have included a few examples of Hofmann's bacillus.

In examinations of diphtheria convalescents he states that he often found *B. diphtheriae* which showed Neisser's granules, but was no longer virulent.

His conclusion was that non-virulent *B. diphtheriae* were botanically identical with the virulent forms, but that the former were of no epidemiological significance.

Development of Antitoxin in the Horse Immunized with Non-Virulent Strains.

The writer (Arkwright, 1910) recorded the production of antitoxin in a horse immunized with filtered broth cultures of two non-virulent strains derived from contacts. The antitoxin content of the horse's serum before inoculation was almost exactly one-quarter of a unit per c.c. After about a litre of filtrate from the first strain had been injected in repeated doses, the antitoxin content had risen to 4 units per c.c. The filtrate from the second strain was then injected at suitable intervals, and the antitoxin content rose to 25 units per c.c.

This experiment was not successful when further attempts were made to repeat it with other horses.

It has, however, never been conclusively demonstrated that the non-virulent strains are really the same kind of bacilli as the virulent *B. diphtheriae*, and, *a fortiori*, it is quite unproved that the non-virulent strain readily changes into the virulent or *vice versa*.

Against the unity of the two kinds of strain may be urged the following arguments :

1. The non-virulent *B. diphtheriae* strains usually, but not always, resemble in morphology a very long type of *B. diphtheriae*, and are not so varied as the virulent strains.

2. Most other pathogenic organisms have affinities with groups of bacteria which closely resemble them, but which are not pathogenic. Differentiation in such cases is often only possible by serological methods.

3. Non-virulent strains are, on the whole, rarely found in cases of clinical diphtheria, and if the average of a large number of observations is considered, cannot be shown to occur more frequently in " contacts " than in the general healthy population.

4. There is abundant evidence that as a rule diphtheria bacilli which persist in the fauces of convalescents often retain their virulence undiminished, and may remain fully virulent for weeks or months.

5. The virulent strains of *B. diphtheriae* which occur in any single outbreak are usually of a fairly uniform degree of virulence, and some workers have found little or no evidence of variations in virulence, in spite of a careful and extensive series of observations.

6. There is no known method by which a virulent strain of *B. diphtheriae* can be converted into a non-virulent strain, or *vice versa*, and almost all attempts in this direction have completely failed.

Occasionally the change appears to have taken place after animal passage or culture, but it has never been possible to detect the cause and repeat the occurrence.

Facts in Support of the View that Virulent B. Diphtheriae are not the Same Kind of Bacillus as the Non-Virulent B. Diphtheriae.

In support of the statement that non-virulent *B. diphtheriae* are not especially closely associated with diphtheria, Graham-Smith (1908*n*) has brought forward a large number of figures collected from careful records showing the frequency with which non-virulent *B. diphtheriae* occur in healthy persons, whether associated with diphtheria or not. He found that, on the average, non-virulent *B. diphtheriae* occurred in the mouths of 1 to 2 per cent. of healthy persons, or in the throat or nose of 2·6 per cent. He himself examined 1,200 persons who were more or less exposed to diphtheria, but who were not suffering from the disease, and found non-virulent *B. diphtheriae* in 15, or 1·25 per cent. He concluded that probably a non-virulent *B. diphtheriae* in a healthy person was of no importance, and was, perhaps, really an entirely distinct bacillus from the virulent *B. diphtheriae.*

The same observer (1908*h*), during the Cambridge epidemic in 1904, examined 1,094 persons in seven schools for the presence of *B. diphtheriae:* 29 persons (2·9 per cent. of the whole), notified as suffering from diphtheria, yielded virulent strains, and none yielded non-virulent *B. diphtheriae;* whereas of the contacts, 33 (3 per cent.) yielded virulent strains, and 11 (1 per cent.) non-virulent strains.

The 62 virulent strains, therefore, were obtained in about equal numbers from the cases of diphtheria and the contacts, whereas the 11 non-virulent strains all came from the contacts. The cases of diphtheria did not yield one. Of course some of these persons may have harboured both varieties, although only one was detected.

Büsing (1907), whose observations are quoted above, states that amongst non-contacts 16 per cent. of the children and 10·4 per cent. of the adults were carriers of non-virulent *B. diphtheriae.*

The virulence was tested by injecting a loopful of growth off a culture on solid medium.

Further evidence on this question is derived from virulence tests made repeatedly both during the disease and during convalescence.

Thus, Park and Williams (1896) examined the strains of *B. diphtheriae* isolated from patients during the disease and at different stages of convalescence. They found no evidence of diminished power of toxin production by the *B. diphtheriae* whilst the patients retained the bacilli.

Prip (1901) also found that in eight convalescents the bacilli retained their full virulence up to the time of final disappearance.

In one case the virulence was shown to be undiminished up to the three hundred and thirty-fifth day.

Similar observations have frequently been made by other workers, though rarely a non-virulent bacillus has been observed to replace a virulent strain.

Seligmann (1911) isolated *B. diphtheriae* from some persons as long as three to five months after it had first been discovered, and always found that the strain remained virulent.

It is argued that if virulent *B. diphtheriae* frequently became non-virulent, strains of intermediate virulence would frequently occur. Graham-Smith (1904) isolated *B. diphtheriae* from 113 out of 117 persons (patients and contacts) during an epidemic. Of these, 87 were fully virulent, and killed rapidly in doses of 2 c.c.; 25 were completely non-virulent. One strain did not kill the guinea-pig in twelve days, but this strain grew poorly in broth.

That this uniformity has not always been found is seen from some of the above-mentioned observations, *vide* pp. 195, 196 (Arkwright, Pennington).

Conclusion.

In spite of the facts pointing to the *average* frequency of non-virulent *B. diphtheriae* not being much greater in "contacts" than in "non-contacts" when large numbers of observations are considered, and in spite of the lack of proof of diminishing virulence in convalescents, there is, nevertheless, some striking evidence of the excessive frequency of non-virulent *B. diphtheriae* in contacts and convalescents in some outbreaks, and even of the occasional association of non-virulent *B. diphtheriae* with clinical diphtheria. It is therefore probable that the causal connection between carriers of non-virulent *B. diphtheriae* and clinical diphtheria cannot be neglected, although the non-virulent strains are possibly of less importance.

OCCURRENCE OF THE B. DIPHTHERIAE IN THE LOWER ANIMALS.

Except for the isolated observations in which virulent *B. diphtheriae* has been found in association with a local unhealthy condition in the horse (Cobbett, 1900) and in the dog (Brandt, 1908), the only domestic animal which has been shown to be a source of danger to man is the cow.

In at least two separate outbreaks of diphtheria the bacillus has been isolated from milk. In such cases, however, the cow is not necessarily the source of the bacilli, as the milkman may be a carrier, and may directly infect the milk.

Virulent *B. diphtheriae*, however, has been found in sores on the cow's teats, but in these cases probably the bacilli have been inoculated from the milker's hands on to pre-existing ulcers, as in the cases recorded by G. Dean and Todd (1902), and Marshall (1907).

The diphtheria of fowls and pigeons is due to an entirely different kind of virus (filter-passer), and the bacillus with which it is sometimes associated is not the true *B. diphtheriae* (Dean and Marshall, 1908).

OCCURRENCE OF THE B. DIPHTHERIAE IN INANIMATE OBJECTS.

It may not be amiss to conclude this chapter with some notice of the recovery of the diphtheria bacillus from inanimate objects associated with cases or carriers.

No doubt the bacillus can remain alive for a long time in a partially dried state.

It can commonly be subcultured from dried-up agar cultures which have been kept at room temperature for three to six months.

H. Cristiani (1906) claims to have found the *B. diphtheriae* in considerable numbers on pencils which had been sucked by diphtheria carriers, and then put away in boxes for fifteen days. A few *B. diphtheriae* were found after forty-two days on an inkstand. He appears, however, to have trusted entirely to the morphology in identifying the bacilli found, and to have made no carbohydrate or virulence tests.

Other observers have frequently failed to isolate *B. diphtheriae* from pencils used by carriers.

Seligmann (1911), however, states that virulent *B. diphtheriae* was recovered in one instance from the cracks between the boards of a floor into which a child who was suffering from commencing diphtheria had vomited some days before, although the room was twice disinfected with formalin in the interval.

Soiled handkerchiefs, etc., may readily convey the disease (Park and Beebe, 1895). Thus, *B. diphtheriae* has been found alive after eleven weeks on a handkerchief (Trevelyan, 1900).

Wright and Emerson (1894) cultivated virulent *B. diphtheriae* from the dust of a hospital ward.

Weichardt (1900) examined 50 samples from a sick-room and 250 from other parts of the house, with the result that *B. diphtheriae* was found on three articles which were directly soiled by the patient—viz., a bottle, a neck-cloth, and a carpet at a spot 20 inches from the patient's mouth.

Hill (1902) examined 528 swabs from bedding, floors, etc., and found only 14 doubtful non-virulent bacilli.

It is therefore quite possible that, under favourable circumstances, the bacillus often remains alive outside the body for a considerable period, and may then conceivably cause fresh infections. However, the latter event is probably rare.

IV. PERSISTENCE.

The length of time during which the specific organisms continue to inhabit the mucous membrane of the fauces or nose in an infected person is a question of great importance for the spread of the disease.

In the case of healthy contacts, the date at which the bacilli first invade the fauces, etc., is generally unknown, and the period of persistence must be reckoned from the date at which the *B. diphtheriae* are first detected. In recorded observations on convalescents the persistence is dated either from the onset of the disease or from the disappearance of the membrane or other local exudate from the site of the infection.

With regard to convalescents, it is important to know what percentage of patients retain the bacilli for different periods of time after the disappearance of the local disease.

Since about 50 per cent. of patients have lost the bacilli by the time the local membrane has disappeared, the number of convalescents who retain the bacilli for any given time after the disappearance of the membrane is a much larger fraction of the number of early convalescents than of the total number of cases of illness. If those in whom the bacillus persists for one month are 7 per cent. of the whole, they are about 14 per cent. of those who still " carry " at the beginning of the convalescence.

Most statistics appear to show that healthy contacts who are carriers retain the bacilli in the fauces for the same length of time as patients who still harbour the bacillus at the commencement of convalescence. As has been pointed out above, the distinction between these two classes is very often difficult to make, and often in records of observations on large numbers of school-children, those who have had mild sore throat or nasal catarrh without much fever are classed with healthy contacts.

In many epidemics careful observations have been made on the length of time during which the persons in whom the *B. diphtheriae* has been found retain the organism in the throat or nose.

Graham-Smith (1902) found that the mean duration of persistence for hospital patients was twenty-eight days from date of notification. One child retained the bacillus up to eighty-seven days.

In a subsequent epidemic he (Graham-Smith, 1904) calculated that the mean duration in the throat of virulent *B. diphtheriae* amongst notified persons who recovered, was thirty-six days, of non-virulent, fifteen days, counting from the first day when the *B. diphtheriae* was found, to the first of three consecutive negative examinations.

Scheller (1906) examined a large series of convalescents who were found to harbour *B. diphtheriae* after the throat had become healthy in appearance.

The bacillus was found for the last time at different periods of convalescence in the following numbers of persons:

Under	10	days in	75	persons	(23	per cent.)	of those examined.
Over	11	,,	264	,,	(77	,,)	,, ,,
,,	21	,,	119	,,	(35	,,)	,, ,,
,,	31	,,	62	,,	(18	,,)	,, ,,
,,	41	,,	35	,,	(10	,,)	,, ,,
,,	51	,,	26	,,	(7·6	,,)	,, ,,
,,	61	,,	18	,,	(5	,,)	,, ,,
,,	90	,,	8	,,	(2	,,)	,, ,,

If the numbers were calculated as percentages of the whole number of patients, the duration would appear much less—*e.g.*, probably only about 9 per cent. of cases were still infected after thirty-one days; 2·5 per cent. were still infected after sixty-one days; 1 per cent. were still infected after ninety days.

Prip (1901) examined a series of hospital patients at ten-day intervals.

Of 654 patients, 309 still retained the bacillus after disappearance of the membrane.

The bacillus was found for the last time in the following numbers of convalescents at the different periods:

Between 1 to 10 days in 118—*i.e.*, 38·2 per cent. of the convalescents, or 18 per cent. of the total cases.

Between 10 to 20 days in 93—*i.e.*, 30·4 per cent. of the convalescents, or 14·4 per cent. of the total cases.

Between 20 to 30 days in 51—*i.e.*, 16·5 per cent. of the convalescents, or 7·8 per cent. of the total cases.

Between 30 to 60 days in 41—*i.e.*, 13·3 per cent. of the convalescents, or 6·3 per cent. of the total cases.

Between 60 to 90 days in 4—*i.e.*, 1·3 per cent. of the convalescents, or 0·6 per cent. of the total cases.

Between 90 to 120 days in 2—*i.e.*, 0·65 per cent. of the convalescents, or 0·3 per cent. of the total cases.

He mentions the case of a woman with ear discharge due to otitis media, from which virulent *B. diphtheriae* could be isolated seventy-three days after disappearance from the fauces.

Prip also examined a series of sixty patients after their discharge from hospital.

The *B. diphtheriae* was found for the last time—

Under	1	month	from disappearance	of membrane	in	13	persons.
Over	1	,,	,,	,,	,,	20	,,
,,	2	,,	,,	,,	,,	11	,,
,,	3	,,	,,	,,	,,	6	,,
,,	4	,,	,,	,,	,,	5	,,
,,	5	,,	,,	,,	,,	2	,,
,,	8	,,	,,	,,	,,	1	,,
,,	11	,,	,,	,,	,,	1	,,
,,	22	,,	,,	,,	,,	1	,,

In some of these cases the observations were not carried to the limit, because circumstances prevented the examination being continued.

He narrates the history of a girl eight years old who had a mild attack of diphtheria, and subsequently became a convalescent carrier. This child in all probability gave the disease to a series of children, one of whom was infected eighty-four days after the membrane had disappeared from the carrier's throat.

Fibiger (1897) records the occurrence of 9 cases of diphtheria in a school. Of 134 contacts who were examined, 22 were found to be carriers, and after isolation of the latter the epidemics stopped. One convalescent boy of eleven years old retained fully virulent *B. diphtheriae* in the throat for nine months after his attack of diphtheria.

Wesbrook (1898) mentions the persistence of *B. diphtheriae* in the throat of one boy 115 days after it had first been found there.

Hewlett (1896) records the case of a boy of fifteen years in whom the *B. diphtheriae* persisted for twenty-two weeks from the first date of its discovery during the acute attack of diphtheria.

At the end of that time he showed that the bacillus was still virulent. In the Massachusetts State Board of Health Report for 1899 (p. 673) a summary is given of four years' work. The Report gives 27·4 days as the average duration of the persistence of the *B. diphtheriae* in the throat from the earliest symptom of the disease in 691 cases.

Tjaden (1907), at Bremen, found that adult convalescents lost the bacillus more rapidly than children, after the expiration of the first three weeks from the onset of clinical symptoms. He took three age-groups, and calculated the percentage in which the *B. diphtheriae* had disappeared at different periods.

Age in Years.	Retained the B. Diphtheriae from Onset.	
	Three Weeks.	Five Weeks.
1 to 6	24·9 per cent.	7·1 per cent.
6 ,, 14	24·8 ,,	8·3 ,,
Over 14	25·2 ,,	2·6 ,,

Park and Williams (1908) repeatedly examined 605 consecutive cases of diphtheria.

Within 3 days after disappearance of the membrane 304 cases were free from *B. diphtheriae.*
Within 7 days after disappearance of the membrane 176 cases were still infected.
Within 12 days after disappearance of the membrane 64 cases were still infected.
Within 15 days after disappearance of the membrane 36 cases (5·7 per cent. of the total cases) were still infected.
Within 3 weeks after disappearance of the membrane 12 cases (1·9 per cent. of the total 605 cases) were still infected.
Within 4 weeks after disappearance of the membrane 4 cases (0·8 per cent. of the total 605 cases) were still infected.
Within 9 weeks after disappearance of the membrane 2 cases (0·3 per cent. of the total 605 cases) were still infected.

Park met with a case which yielded virulent *B. diphtheriae* during eight months.

Wesbrook (1905) found that in clinical cases of diphtheria the dates at which the *B. diphtheriae* could no longer be detected were as follows:

By the	7th	day in	3	per cent.	*B. diphtheriae*	had	disappeared.
,,	14th	,,	27	,,	,,	,,	,,
,,	21st	,,	51	,,	,,	,,	,,
,,	28th	,,	83	,,	,,	,,	,,
,,	35th	,,	93	,,	,,	,,	,,
,,	70th	,,	100	,,	,,	,,	,,

One girl of ten still retained virulent *B. diphtheriae* for 109 days, and this strain was proved to be virulent on the seventy-second day. A school-teacher who had had diphtheria still harboured fully virulent *B. diphtheriae* on the eightieth day.

Prip (1901) records the persistence of a virulent bacillus for 335 days. Graham-Smith collected seven recorded cases in which virulent bacilli persisted for over 100 days, and another series in which only the morphology was taken into account.

Amongst these latter is a case recorded by Prip in which the bacillus persisted 669 days in one person; and, in all, eighteen cases are mentioned, with a persistence of over 100 days each, of which eight retained the bacillus for over 200 days.

Persistence in Healthy Carriers.

Most observers appear to be of opinion that "healthy carriers" retain the *B. diphtheriae* for as long a period, on the average, as convalescents.

Graham-Smith (1902) states that a few healthy children in a certain outbreak retained the *B. diphtheriae* for a long time—in one case up to the eighty-seventh day.

Kober (1899) gives the period of persistence as usually less than twenty-eight days.

Sacquépée (1910), on the other hand, expresses the opinion that the persistence in healthy carriers is generally brief.

The figures dealing with persistence in healthy carriers are not so numerous as in the case of convalescents, since persons belonging to the former class are not usually in hospital, and consequently are less often examined.

Graham-Smith (1908*p*) constructed a table comparing the persistence of *B. diphtheriae* in notified cases and healthy carriers, according to whether the bacilli were virulent or non-virulent.

He shows that of 67 notified cases, in 43 the virulent bacilli did not persist more than thirty days; and of 50 healthy contacts, 27 ceased to harbour the bacillus at the same period.

The average duration of persistence for notified cases was 31·6 days for virulent, and 18·5 days for the eleven non-virulent strains; whereas for healthy contacts the persistence was 36·4 days for virulent, and 30·0 days for non-virulent.

The difference between the two groups was, therefore, not very great.

Intermittence.

It is well known that if a convalescent is examined at intervals of a few days, a single examination may give a negative result, and a few days later a positive result may be obtained. The rule is therefore generally accepted that three, or at least two, consecutive negative examinations should be made before a carrier may be discharged from isolation. Even after three negative results the bacillus may occasionally reappear in the throat, but for practical purposes three " negative " examinations at intervals of four or five (or preferably seven) days should be made, and may be taken to indicate freedom from bacilli.

It is, however, important to decide on some criterion according to which the convalescent or healthy carrier may, for practical purposes, be considered free from the bacilli after certain tests.

The criterion adopted is arbitrary, and only approximately corresponds to the facts.

The following tables illustrate the results obtained by repeatedly swabbing a class or family of contacts.

The school class, containing thirty-seven girls and thirty-seven boys respectively, was examined repeatedly by Ustvedt (1906).

	1903 : Sept. 28	1903 : October.							1903 : Nov. 5	1904 : March 1
		13	15	17	19	21	23	26		
Girls 1 ..	+	+	+	0	+	+	+	+	0	+
,, 2 ..	0	0	0	0	0	0	0	0	0	+
,, 3 ..	+	+	+	+	+	+	+	+	0	0
,, 4 ..	0	0	0	0	0	0	0	+	0	0
,, 5 ..	+	+	+	+	+	+	+	+	+	+
,, 6 ..	0	0	0	+	0	0	0	0	0	0
,, 7 ..	+	0	0	0	+	0	+	0	+	0
,, 8 ..	0	+	+	+	+	+	+	+	+	0
,, 9 ..	+	0	0	0	+	+	+	0	0	+
Boys 1 ..	0	+	+	0	0	+	0	0	0	0
,, 2 ..	0	0	0	0	0	+	0	+	0	0
,, 3 ..	0	+	0	0	0	0	0	0	0	0
,, 4 ..	0	0	0	0	0	0	0	+	+	0
,, 5 ..	0	0	+	+	+	0	0	0	0	0

The remaining sixty children gave negative results throughout.

Intermissions in the series of positive results obtained by swabbing diphtheria convalescents are very often noticed when repeated observations are made.

Cobbett (1901*a*) found that 37 per cent. of cases yielding negative results were followed by a positive.

Graham-Smith (1908*r*) made observations on 331 convalescents and carriers. Of these, 127 (38·3 per cent.) gave positive results following one or two negative.

Temporary and Chronic Carriers.

Diphtheria carriers have usually been classified as temporary or chronic, according to the length of time during which the bacilli persist. A chronic carrier then may be defined as one who is known to have harboured the bacilli for a longer period than three months.

The records of systematic examinations of convalescents quoted above show that not more than 1 or 2 per cent. continue to be carriers after ninety days from the onset (Scheller, 1906), and the percentage may be only 0·3 per cent., according to Prip's (1901) large series of hospital cases. In another series Prip found altogether six persons who were still carriers three months after the disappearance of the membrane out of sixty who left hospital in an infective condition four to six weeks after the onset of the attack. If only virulent *B. diphtheriae* were taken into consideration, the number of chronic carriers would be reduced.

Graham-Smith (1902), out of 519 persons, found only one who retained the virulent *B. diphtheriae* up to the eighty-seventh day.

There is abundant evidence that the bacilli may retain a high degree of virulence, even when a long period has elapsed since the carrier was suffering from diphtheria or was in contact with a clinical case of the disease.

In some cases the virulent *B. diphtheriae* has apparently been replaced by a non-virulent strain after a long period.

Prip (1901) examined the virulence of *B. diphtheriae* isolated at different times from numbers of convalescent carriers. He found the bacillus fully virulent in cultures made 13 to 335 days after the membrane had disappeared.

He recorded two cases in which the bacilli isolated in the first instance were virulent, but subsequently a non-virulent strain was found. In one case the strain isolated was virulent after 142 days, but that found after 256 days was non-virulent. In the other case a virulent strain was found thirteen days after disappearance of membrane, and a non-virulent 280 days later, or 293 days from the date at which the throat was free from membrane.

In chronic carriers, therefore, the strain of *B. diphtheriae* may be either virulent or non-virulent, and this is true whether the nose or throat appears to be healthy, or whether chronic thickening or muco-purulent secretion is present.

The occurrence of non-virulent *B. diphtheriae* in late carriers has been further described on p. 196.

Chronic Diphtheria.

Some of the persons classed as " chronic carriers" should more correctly be called cases of " chronic diphtheria."

Many chronic carriers have nasal discharge or enlarged and unhealthy tonsils, but the cases of chronic diphtheria most widely recognized as such are the cases of chronic fibrinous or membranous rhinitis associated with diphtheria bacilli. Persons who are the subjects of this affection appear to be in good general health, but the membrane lining the nares is usually quite easily seen, though it is variable in amount from time to time.

Goodall and Washbourne (1908) mention chronic cases of diphtheria in which membrane is continually reformed after separation, and state that this process may go on for as long as six weeks, or even nine months.

Park (1892), Reichenbach (1899), and Scheller (1906) reported cases of chronic fibrinous rhinitis from which virulent strains of diphtheria bacilli were isolated.

Lack (1899) gives a clinical description of fibrinous rhinitis, and says that the duration of the disease is four to eight weeks or more. There were 16 cases of this form of disease among 700 new patients in one year at a children's hospital, and all the strains of *B. diphtheriae* isolated from his cases were virulent. One of his cases did not recover for eighteen weeks. He thinks a case of fibrinous rhinitis is apt to cause the same form of disease in others, but not ordinary diphtheria.

In a later paper (1906) the same author brings forward evidence to disprove the association of *B. diphtheriae* with atrophic rhinitis, which had been asserted by Belfanti and Symes.

Forbes and Newsholme (1912) record cases of membranous rhinitis due to virulent *B. diphtheriae* which were in close relation with, and were probably the cause of, a school outbreak of diphtheria.

Also, E. Neisser (1902) reports the infection of three children in one family by a nursemaid (twenty-two years old) who had suffered from frequent attacks of hoarseness associated with virulent *B. diphtheriae.* Her brother had diphtheria when she was eight years old. Neisser considers it probable that she had been a carrier ever since—*i.e.*, for fourteen years—the throat and larynx being affected with chronic inflammation which was subject to periodic exacerbation.

Cuno (1902) gives an account of an epidemic of diphtheria in a children's hospital, which he attributes to one of the nurses having a chronic laryngitis associated with *B. diphtheriae.*

Occasionally chronic otorrhœa is associated with virulent *B. diphtheriae,* as in a case recorded by Prip, in which virulent *B. diphtheriae* were isolated from ear discharge seventy-three days after the membrane had disappeared from the throat.

A small outbreak is described by Graham-Smith (1904), in which an otorrhœal discharge containing virulent *B. diphtheriae* apparently infected seven persons, three of whom suffered from clinical diphtheria.

Cases of chronic diphtherial infections of the skin are related by Dawson (1910) and Cuno (1902), and are mentioned on p. 179.

V. INFECTIVITY OF CARRIERS.

Diphtheria was recognized as an infectious disease when it was described by Bretonneau in 1826 ; but though in some outbreaks early in the nineteenth century five or six persons out of one family appear to have died of the disease, its infectiousness was sometimes doubted, and several physicians (Peter and Trousseau) made experiments on themselves with a view to decide the question. Trousseau rubbed a lancet on the membrane from the patient's throat, and then pricked his lip and soft palate in several places with the instrument. He also states that Peter made similar experiments on himself.

These attempts at inoculation of diphtheria into human beings were unsuccessful, but it is not now possible to determine whether all the epidemics of so-called "diphtheria" at that time were really due to the same disease. Even at the present day, it is often difficult or impossible to decide the nature of a sore throat without bacteriological examination ; and, indeed, the definition of diphtheria now includes the causation of the pathological state by the *B. diphtheriae* (although it may not be invariably possible to demonstrate its presence).

The infectivity of the disease is not very high when one takes account only of the cases of considerable local inflammation or membrane formation. It often happens that only one or two persons in a family are attacked by decided symptoms of the disease, even when several persons of susceptible age are present.

Diphtheritic membrane coughed directly from a patient's throat into the mouth or eye of another has frequently caused diphtheria, though it does not always do so.

The feeble spreading power appears, at any rate, in part, to be due to the insusceptibility of a large proportion of the population on account of a general or local immunity, which is frequently only temporary or partial. The local bacteriological flora may have some importance.

Cave (1912) has recently brought forward some observations which suggest that children who harbour the bacillus of Hofmann are immune to diphtheria, but his evidence is not convincing.

In some carefully investigated diphtheria epidemics it is remarkable how long a carrier may remain in a community of children without giving rise to a single clinical case of diphtheria (Seligmann, see Section III.), or to any considerable number of carriers. On the other hand, Scheller maintains that as a rule every person in close contact with a case of diphtheria sooner or later becomes a carrier.

These apparently rather contradictory observations are probably not really antagonistic, the differences being accounted for by variations in the factors involved.

The transmission of the disease from one person to another may be considered as taking place in three stages :

1. The dissemination of the bacilli from the throat or nose.

2. Their reception on the mucous membrane of another person, and establishment there.

3. The production of definite local morbid changes in the tissues of the new host.

Of these three processes, the second is perhaps the simplest and most regular in action.

Persons of all ages may become carriers of *B. diphtheriae*, if they are in close relation with those who are distributing the bacilli. But though carriers may be very numerous in a community, and though all who are exposed to infection may become carriers, yet the total number of carriers at one time during an epidemic seldom exceeds one-fifth or one-third of the community invaded. This is largely due to the short period during which many of these carriers are infected. The number of carriers appears to vary in different outbreaks from nil to at least ten times the number of cases of disease.

The majority, or a large proportion, of carriers invaded by the bacillus either have catarrhal symptoms at the time, or give a history of a recent sore throat. The frequency of mild disease in carriers is also shown by the large proportion who may be picked out by an experienced medical man by mere inspection of the persons implicated in an epidemic.

The formation of carriers is not entirely a haphazard process due to the entry of a person within the range of distribution of a case of diphtheria or a carrier.

At certain ages persons are more liable to become carriers (Thomas, 1904), and more than one observer has found that sex has an influence, carriers being two or three times more numerous among males than females.

The distribution of the bacilli by cases of the disease or carriers most commonly occurs, in all probability, by such actions as coughing, sneezing, kissing, etc., by which the host can hardly fail to disperse large numbers of bacilli in droplets of moisture.

There can be no doubt, too, that drinking-cups, pencils, musical instruments, etc., are ready methods of distribution.

Though attempts to find *B. diphtheriae* on pens or pencils which have been used by carriers have often failed, some observers have detected their presence on such articles (see p. 202).

It seems probable, however, that though these intermediate means of distribution should not be forgotten, still, the more direct methods of dispersion are most commonly effective.

In a certain number of carriers *B. diphtheriae* can be readily found in the saliva obtained by making a patient spit into a tube, showing that there are very large numbers of *B. diphtheriae* in the mouth available for distribution. The writer examined the saliva of twenty-four diphtheria convalescents who were still infected with the diphtheria bacillus one to three months from the onset of the attack of diphtheria. The specimens of saliva were obtained by causing these persons to spit into a sterile test-tube. From the saliva of ten of these persons bacilli giving the cultural appearances and reactions of *B. diphtheriae* were isolated by plating on serum agar. Seven of these strains were shown to be virulent, and two to be non-virulent, whilst the remaining strain was probably identical with the non-virulent strain isolated from the throat at the same time.

There is some evidence that comparatively few carriers are able at any one time to distribute the bacilli freely, and this may easily be accounted for by the difference in the numbers present in the case of different carriers, by their presence in the saliva, the occurrence of nasal discharge or otorrhœa, and the habits of the patient—*e.g.*, whether subject to sneezing, coughing, and whether clean or addicted to sucking pencils, etc. Nasal or aural discharges containing *B. diphtheriae* may communicate the disease, and cases of chronic membranous rhinitis are well known to cause the spread of diphtheria (Cobbett, 1901*c*; Forbes and Newsholme, 1912). This difference amongst carriers, which is *a priori* probable, is made still more so by the fact that the detection and exclusion from a school class of a few carriers will often stop an epidemic, although a bacteriological examination of all the scholars has not been made. Probably a considerable number of healthy carriers still remain in the class, but appear not to be efficient distributors, since no fresh cases of diphtheria occur.

Some writers, indeed, are of opinion that it is the nasal carrier who constitutes the most important and the most persistent distributing agent.

A single case will often apparently effect the invasion of large numbers of persons, but it is difficult to be certain how many are infected directly.

Prip records that of fifty-two carriers who left hospital still harbouring *B. diphtheriae*, only three caused return cases. He does not record, however, how many children or susceptible persons they came into contact with, nor the number of persons who received the bacillus and themselves became healthy carriers.

The third factor in the production of disease by carriers concerns the ability of the *B. diphtheriae* to produce definite disease in a given person whose nose or throat it has invaded. It is often difficult to be certain whether a carrier has had any definite local disease due to the *B. diphtheriae* or not, for the changes may be slight or have ceased at the time of observation. Occasionally a carrier whose history dates from a slight sore throat a few weeks previously has a second attack whilst under observation. It is then often impossible to tell whether either attack or both are really diphtheria, since the patient has the *B. diphtheriae* on the mucous membrane all the time. Not infrequently it happens that a carrier with no history of the disease develops an attack of diphtheria either spontaneously or as the result of an operation for removal of tonsils, adenoids, or nasal polypi.

Whether a person receiving and retaining the *B. diphtheriae* in the throat or nose develops diphtheria appears to depend on the local or general power of resistance. It seems probable that all grades of susceptibility exist which determine whether those harbouring the specific organisms will show local lesions of varying degrees of intensity or none at all.

Wassermann (1895) found that the blood serum of many normal persons had a small degree of antitoxic power, and argued from this fact that these were probably the persons who were insusceptible to *B. diphtheriae*, and were liable to become carriers.

The instances cited above of carriers subsequently developing diphtheria are against this view, or rather against the idea of absolute immunity occurring in this way. Partial antitoxic immunity is not improbable.

General Susceptibility due to Impaired Health.

Seligmann (1911) found that in a large institution for children, orphans, etc., cases of diphtheria often occurred when influenza or whooping-cough broke out. He attributes this sudden appearance of diphtheria to the lowered resistance of the children, which permitted the *B. diphtheriae*, which was already present in carriers, to exercise a more definite effect in producing pathological lesions and clinical symptoms.

Influence of the Virulence of the Strain.

Another factor which may influence the frequency with which the disease occurs in carriers of the bacillus is the virulence of the strain of *B. diphtheriae* which is present.

The degree of importance to be attached to the presence of the completely non-virulent type of *B. diphtheriae* has been discussed in the last section. With regard to the virulent type of the *B. diphtheriae*, evidence is forthcoming that the virulence of different strains of undoubted virulence varies within wide limits, as tested on the guinea-pig (Arkwright, 1911).

The significance of these variations in virulence is not at present sufficiently understood to enable us to explain on this basis the occurrence of clinical diphtheria in one carrier and not in another. Moreover, it has been observed that all strains of bacilli isolated from cases during some epidemics are of similar pathogenicity, and a strain isolated from a healthy carrier may be highly pathogenic for laboratory animals.

Epidemics occasionally occur in which hardly any healthy carriers are found (Seligmann, 1911)—that is to say, every person found to be harbouring the *B. diphtheriae* has, or has recently had, a sore throat.

A small epidemic which came under the observation of the writer illustrates this point. The outbreak occurred in a school boarding-house. Eight boys were attacked with diphtheria in the course of about six months. In all the cases of illness the *B. diphtheriae* was present, and there was also severe sore throat with deposit in the fauces. All the boys and staff, sixty in number, were examined on three occasions during this period. Only one healthy carrier was found, and in his case the strain of *B. diphtheriae* was non-virulent. Five of the strains from different boys were isolated, and all but one proved to be of low virulence (0·1 c.c. of a two-days' broth culture was not fatal to a guinea-pig of 250 grammes, but 2 c.c. killed the animal in four days), the result being controlled by the inoculation of a guinea-pig with antitoxin, in addition to the dose of culture.

It has been pointed out that in some houses diphtheria has been particularly liable to occur. Feer (1894) gave instances of the occurrence of so-called diphtheria houses. He attributes the recurrence of disease to the dark and damp character of these dwellings, and he thinks these factors were likely to increase the susceptibility of the inhabitants. It seems doubtful if this is a complete explanation. In some cases the association of the household with a chronic carrier is probably the cause.

The intimate association of carriers with cases of diphtheria has been repeatedly established by the most thoroughly conducted investigations, and it may be of interest here to discuss this association in the light of two dominant views which have been held regarding the natural history of the disease.

The older and more obvious view is that the severe cases of diphtheria are the central points, as it were, from which infection spreads. Healthy persons in the *entourage* of such cases are invaded by the bacillus dispersed by the patients, and become carriers, who in their turn may possibly become centres of infection, but much less frequently so. The actual cases of diphtheria are regarded as in every sense the important factors in epidemics and the most efficient distributors of infection.

According to the other view, certain carriers who are never known to have had the disease, or have for some time completely recovered, are regarded as the most important factors in the natural history of the disease by reason of their habit or function of distributing *B. diphtheriae* amongst those in daily converse with them. Occasionally such distributors may be actually suffering from chronic diphtheria.

The clinical case of diphtheria is, on this view, rendered a less efficient distributor of the disease, because, on account of his illness, he is isolated or confined to bed.

It is not suggested that the case of diphtheria is an unimportant source of infection, for a patient has often infected nurses and other patients in the same ward.

No doubt in communities where isolation is less practised, cases of diphtheria constitute a more serious source of infection than in communities under good hygienic conditions where isolation of cases of infective illnesss is carefully carried out.

In any case, it seems probable that some cases of diphtheria and some carriers are much more efficient distributors than others.

According to the view which regards the carrier as the more important distributor of *B. diphtheriae*, the origin and course of an ordinary epidemic would be traced in the following manner: A chronic carrier surviving from another epidemic would, perhaps, cease to distribute bacilli for a time, until some factor, such as an attack of catarrh, caused him or her to cough or sneeze, or by means of a nasal discharge infect his surroundings. In this way other carriers would arise, all of whom would not distribute with equal efficiency. Some of these carriers would actually develop diphtheria sooner or later, and in the usual state of affairs in well-organized communities would cease to distribute efficiently on account of isolation.

In many outbreaks numerous carriers would have arisen before cases of diphtheria began to appear.

It might even be that the cases of diphtheria which arose were in persons who were only occasionally associated with the community of distributing carriers—as, for example, in the case of a single child being ill with diphtheria in a school class in which no carriers are found, the infection being from some source at home, or at any rate not within the class.

In a case of this kind no healthy carriers may be found in the class. In other outbreaks a large proportion of the class may become carriers before a clinical case of diphtheria occurs. According to this view, then, the cases of diphtheria are perhaps not the most important factors in the epidemiology of diphtheria epidemics from a public health point of view, but the apparently healthy efficient distributing carriers who often continue for a long period, though perhaps intermittently, to disperse *B. diphtheriae* amongst their surroundings must be considered at any rate of equal epidemiological importance. If these persons could be supervised until permanently cured of their infection, fresh epidemics might be avoided. It seems not improbable, as pointed out in the section on Persistence of *B. diphtheriae* in Carriers, that these very chronic carriers are comparatively few.

No definite means has yet been devised for distinguishing an efficient carrier from a harmless one, and such a distinction is probably not permanent. Still, by observing such habits as coughing, or sneezing, or spitting, and examining for the presence of *B. diphtheriae* in the saliva, a more accurate estimate of the harm done by individuals may be gained.

The frequency of carriers in immediate contact with cases of diphtheria may often be explained by the presence in addition of one carrier who is an efficient distributor, and of a number of other carriers who were infected by him before the actual case of diphtheria appeared.

VI. PATHOLOGY OF THE CARRIER STATE.

Little work has been done on the pathology of diphtheria carriers, but many observers have remarked on the frequency of enlarged tonsils and adenoids in carriers (Meikle, 1906, Seligmann, 1911, etc.).

Removal of tonsils has been recommended, and has proved successful in a few cases as a means of making carriers whose throats alone yielded bacilli, cease to carry. These successful results suggest that the specific germs frequently inhabit the tonsillar tissues and lacunæ.

In chronic fibrinous rhinitis associated with *B. diphtheriae* membrane is present lining the nasal fossæ.

Virulent *B. diphtheriae* have also been described as occurring in atrophic rhinitis (Symes, 1903), but the observation has not been confirmed, and is probably an unusual occurrence.

Immnuity Reactions in Carriers.

The immunity reactions of the serum of diphtheria carriers have been tested in a number of cases.

E. Neisser (1902) demonstrated the presence of antitoxin in chronic cases of diphtheria, while Wassermann (1895) demonstrated antitoxin sufficient to neutralize ten lethal doses for guinea-pigs in 1 c.c. of the sera of a number of healthy individuals and considered that this antitoxic immunity explained why carriers did not exhibit symptoms of the disease.

Klemensiewicz, Escherich, and Abel (1893) showed that antitoxin was present in the blood of convalescents.

Flügge (1894) and others (Seligmann, 1911), who frequently observed that as a rule only one or very few in a numerous household are attacked with diphtheria, believed that this was due to the others having acquired immunity as carriers (including very mild cases of diphtheria).

Opsonic substances and bacteriolysins have been demonstrated by Tunnicliff (1908) and Lindemann (1910) in diphtheria patients.

It is most probable that carriers are not in a strict sense "healthy," but that most have suffered, and perhaps continue to suffer, from mild diphtheria. In the later stages, and in some cases of temporary carriers, the bacillus probably lives quite on the surface, though often in crypts and recesses of the tonsils, and does not invade the tissues.

VII. TREATMENT.

The medicinal treatment of carriers with a view to freeing them from the bacillus is very unsatisfactory. A great variety of disinfectant mouth washes and gargles have been tried by various observers, but in no case after a fair trial has one antiseptic remedy appeared to produce more rapid disappearance of

B. diphtheriae than another. Amongst the medicaments employed without success are carbolic, iodine, alcohol, chlorine, menthol, thymol, pyocyanase, etc. Injection of antitoxin appears to have no effect in accelerating the disappearance of the bacilli. Antibacillary diphtheria serum has been prepared by L. Martin and by Wassermann, and has been advocated as a local application for the removal of *B. diphtheriae* from the fauces. In other hands this serum has not been found useful. Some years ago a similar serum was prepared by the Lister Institute, but trials made in this country were not favourable, and its preparation was discontinued.

Vaccines of dead virulent *B. diphtheriae* have been employed by some workers with a view to the cure of the carrier condition. Petruschky (1908) appears to have been the first to use vaccines in such cases. Five of his cases ceased to carry while vaccines were being used, but in one case the organisms persisted, and the treatment was continued for a very long time. It was fourteen months before the bacillus disappeared, and the other results were not very conclusive.

Walker Hall and Scott Williamson (1911) have also recorded six cases treated with vaccines. Two of these cases, in which the *B. diphtheriae* had been present for six months and several years respectively, were not cured; but three others, in which the bacilli had been present three months, and one in which they had been present four months, ceased to give "positive" cultures after four or five weekly injections of vaccine.

Forbes, Duncan, and H. P. Newsholme (1912), treated three cases of membranous rhinitis with autogenous vaccines in doses rising from 5,000,000 to 400,000,000 bacilli. The membrane rapidly disappeared after one or two doses of vaccine, but the organisms, though very much diminished in numbers, did not entirely disappear.

These results are sufficiently encouraging to invite further trials.*

On the suggestion of Schiötz (1909), attempts have been made recently to free the fauces from *B. diphtheriae* by introducing living cultures of *Staphylococcus aureus* by means of sprays and swabs applied to the throat.

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* Hewlett and Nankivell (1912) used vaccines consisting of "endotoxin" prepared from diphtheria bacilli by a modification of the Macfadyen-Rowland method, with encouraging results. They treated five cases during the acute stage of the disease, and nineteen other persons who were convalescent or chronic carriers. In the five cases of illness and in twelve carriers, the bacilli quickly disappeared under treatment, and in the remaining six carriers a diminution in the number of bacilli occurred.

Page (1911) records the case of a convalescent carrier who, after three months, still harboured virulent *B. diphtheriae*. After two days of the treatment with staphylococci, *B. diphtheriae* were no longer found, and the examinations continued negative when the case ceased to be observed.

Page (1911) has even recommended using a spray of *Staphylococcus aureus* from the earliest stages of the disease.

Catlin, Scott, and Day (1911) also treated by means of staphylococcus sprays, eight nurses who, without showing symptoms, had become carriers from contact with cases of the disease. No ill-results followed, and the throats are said to have quickly become negative.

De Witt (1911), in an experimental investigation of the subject, found that *S. aureus* cultures did not appear to inhibit *B. diphtheriae* on agar plates. She also found that the *S. aureus* had not much effect on *B. diphtheriae* when injected subcutaneously in the rabbit, but occasionally caused inflammation and suppuration, and appeared to aggravate the disease.

In two human convalescent cases of diphtheria in whom the treatment was begun on the twenty-fifth and fifty-eighth days of the disease, the *S. aureus* appeared to have no ill-effect, but actually to accelerate the cure. In the latter case a negative examination was first obtained after four days' treatment, and no recurrence took place. She suggests that *S. aureus* should not be used during the acute stages, but only when the acute inflammatory stage is past.

The method of treatment advocated by Schiötz, and followed by Page and De Witt, was the following: A fresh twenty-four hours' culture of *S. aureus* in broth was used to swab the fauces daily, and the remainder of the culture was used with a spray by the patient every two hours.

In cases in which the fauces only are infected with *B. diphtheriae,* extirpation of the tonsils is likely to prove very useful as a means of getting rid of the bacilli, as suggested by Pegler (1905).

Even when the specific organisms are found in the nose, removal of adenoids may prove effective. No large series of cases in which these operative measures have been taken has been published, but a fair number of isolated cases have been treated in this way successfully. Before an operation is performed, a dose of antitoxin should be given as a prophylactic, as cases of severe diphtheria in carriers following operation have been reported.

VIII. PUBLIC HEALTH MEASURES.

The methods of dealing with carriers from the public health point of view must be directed towards preventing—(1) the distribution of the bacilli by the carrier, and (2) the direct or indirect association of the carrier with a susceptible individual.

With regard to measures which will prevent the carrier from distributing the bacilli, any means directed to his cure are obviously the most desirable. Cure is, however, difficult or impossible to hasten, and in the meantime thorough local treatment is probably the most useful measure that can be applied.

This includes the application of alkaline lotion and spray to clean the mucous membrane from adherent mucus, and the subsequent use of antiseptics, such as carbolic or iodine. Attention must be given to discharges from the ear or nose, and sore places on face or hands.

Some of those who have most carefully watched diphtheria convalescents from time to time are of opinion that disinfectant gargles, etc., are quite useless. However, this opinion is not held universally. Lentz (1910) considers that adult carriers can use gargles and sprays in such a manner as to render themselves harmless to those in contact with them.

Cobbett (1901*b*) gives an account of seventeen children in an isolation home who were infected with *B. diphtheriae.* In eight the strain had been found to be virulent, and in five non-virulent. The strains from seven of the children were tested on two or more occasions, and in one case as often as ten times during fifteen weeks. It was found that the same children as before yielded virulent and non-virulent *B. diphtheriae* respectively. Antiseptic gargles were used, and cups, etc., sterilized.

By such means it is probable that a large amount of transference of infection from carriers to other persons can be avoided.

There is no doubt that in many cases careful spraying and gargling removes the bacilli from the surface of the throat for a time, and swabs taken within a few hours of this treatment frequently give negative results when a positive is easily obtained on other occasions. Removal of tonsils and adenoids and the use of vaccines, as mentioned in the last section, should have a fair treatment in the case of chronic carriers.

Local treatment by means of living cultures of staphylococcus also deserves further trial.

The most important public health measures are those which secure the discovery and isolation, or at least supervision, of convalescents and healthy carriers as long as they harbour the specific organisms.

For this purpose all contacts with diphtheria cases should be swabbed in nose and throat, and search should be made for other sources of contamination—*e.g.*, nasal discharge, sore places, skin eruptions, whitlows, etc.—all of which must be treated. Negative evidence as to the presence of *B. diphtheriae* should not be accepted as final unless those intimately in contact with the patient have been swabbed at least twice at intervals of four to seven days. Nasal discharges, unhealthy tonsils, or a history of sore throat in carriers must be considered sufficient grounds for enforcing a stricter supervision, just as in the case of actual convalescents. All convalescents and those who are found to be carriers must have the throat bacteriologically examined, and a negative result obtained on at least three occasions with a week's interval, before isolation is relaxed. At least one of these examinations, and preferably all of them, should be accompanied by a separate examination of the nose.

Especial care must be taken in searching for school carriers at the age of five to ten years.

The regulations suitable for schools and institutions where the inmates live and sleep in the building are rather different from those which apply to day-schools, workshops, etc.

In closed institutions no fresh inmate or attendant or member of the staff must be admitted to association with the others till at least one bacteriological examination has been made in order to detect and exclude carriers.

If an outbreak of diphtheria occurs in a school, all immediate contacts, and preferably the whole school, including the teaching staff, etc., should be examined bacteriologically, and if carriers are found, they must be isolated till at least three negative examinations have been obtained. The last examination is to be made a week after removal from those who are giving positive results. In this way serious epidemics may frequently be avoided.

In the case of day-schools, an outbreak of diphtheria in a class should be met by bacteriological examination of all the scholars and teachers. If carriers are found, they should be excluded from school till three negative swabs have been obtained, and the class should be again swabbed at weekly intervals on one or two occasions according to the number of carriers found, etc. If no carriers are found, it is probable that the outbreak is due to infection outside the school.

In cases of diphtheria in the home, and where the disease cannot be traced to the school, all the inmates of the house should be swabbed, and carriers isolated and dealt with as far as possible according to circumstances. Infected school children and teachers must in all cases be kept from school, and the same recommendation applies to milkers, dairymaids, and those engaged in the handling of foods.

All infected adults must be made to use gargles or sprays, and be isolated as far as possible.

Disinfection of schools and scholars' pencils, also soiled linen, drinking-cups, etc., and rooms, especially floors, must also not be neglected, but this does not strictly come into the scope of this work.

Opinions differ as to whether the use of antitoxin is advisable as a prophylactic in epidemics. Undoubtedly, it has been very useful in some cases—as, for instance, when an outbreak occurs in a children's ward at a hospital, in an infants' school, or in a household where a severe form of diphtheria has already occurred, especially if there are small children in the family.

In the case of carriers who have for long yielded cultures reported as "positive," it is well to submit a culture to further investigation with a view to isolation, in order to make sure that the bacillus is properly classed as *B. diphtheriae*, and is not one of the rarer forms of diphtheroid which closely resemble *B. diphtheriae* morphologically.

In the event of the bacillus after isolation proving to be indistinguishable from *B. diphtheriae* culturally, but completely non-virulent for guinea-pigs, the question of the isolation of the carrier arises.

If there is good ground for supposing that only non-virulent *B. diphtheriae* are present—*i.e.*, if the culture appears to contain only one form of *B. diphtheriae*—then sometimes it may be necessary to relax the isolation in certain cases, but under no circumstances should such a child or person be allowed to return to school or to undertake the care of small children. This measure is especially important if an unhealthy discharge from the nose or ear is present. It must be remembered that the presence of non-virulent *B. diphtheriae* in the nose or throat does not exclude the presence of virulent *B. diphtheriae* at the same time.

It is very desirable that, at any rate in the case of those who have carried the *B. diphtheriae* for three or more months, the bacillus should be isolated in order to obtain a more accurate knowledge of the behaviour, persistence, and infectivity of bacilli from these sources.

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CHAPTER V

EPIDEMIC CEREBROSPINAL MENINGITIS

I. INTRODUCTORY.

EPIDEMIC cerebrospinal meningitis is a disease whose history cannot with any confidence be traced to a period more remote than the early years of the nineteenth century. On the authority of Hirsch, to whose account of its various manifestations in the Old and New Worlds up to the year 1884 little that is new can be added, this disease made its first appearance at Geneva in the winter and spring months of 1805. The visitation was reported in its clinical aspects by Vieusseaux (1805), whose statements, taken in conjunction with the pathological findings reported by Mathey, leave us in no doubt as to the character of the disease. It is hardly to be supposed, however, that cerebrospinal meningitis, as we know it, did not manifest itself before 1805; but in the absence of pathological data we must leave to the medical historian the discussion of the probable relationship of certain previously recorded epidemics to acute cerebrospinal meningitis.

The second notification of this disease came, curiously enough, from Massachusetts, where its clinical features and post-mortem findings were described by Daniellson and Mann (1806), who, as we are informed in the excellent monograph by Councilman, Mallory and Wright (1898), were not familiar with Vieusseaux' work.

Since 1805, practically every country in Europe has been periodically visited, while certain areas, particularly of France and Germany, have suffered in a more severe and continuous manner. The history of the disease in America from 1806 down to the outbreak in Boston of 1897 will be found in the above-cited monograph. In tropical countries, also, the occurrence of cerebrospinal meningitis has been reported. Thus, on the African Continent, the disease made its appearance in Algeria about the year 1840, the introduction being in all probability effected by French troops. More recent outbreaks have been reported by Jaffé (1909) in the German Protectorate of Togo, by McGahey (1905) in Northern Nigeria, and by Balfour (1904) in the Eastern Soudan. In 1885 a severe outbreak occurred in the Fiji Islands, and an interesting account of the visitation was presented by Bolton Corney (1888) to the Epidemiological Society of London. For the history of the disease in India, and particularly its prevalence in gaols, the report of Robertson-Milne (1906) should be consulted.

I do not propose, however, to treat even in summary fashion the chronological features of these visitations, as they will be found in full detail in the well-known work of Hirsch (1883) and in the surveys of Bruce Low (1899), Farrar (1906), Councilman, Mallory and Wright (1898), and Busse (1910); but it may be of interest to trace out briefly the history of the disease as it has manifested itself in this country. To Bruce Low's valuable account of the appearances of cerebrospinal meningitis in Great Britain up to the year 1899 we are indebted for much information on this subject. In 1845-46, outbreaks occurred among the Irish Constabulary stationed in Dublin, and certain workhouses (Dublin, Bray, and Belfast) were also visited. Twenty years later (1866) a severe outbreak occurred in Dublin, where the military units both here and at Curragh Camp and elsewhere were attacked, the mortality being high. During the years following this outbreak cases continued to crop up in Ireland. In Dublin another outbreak occurred in 1885-86, when eighty deaths from cerebrospinal meningitis were certified.

Apparently, therefore, as was the case with the early visitations of the disease in France, so in Ireland, the military population suffered severely.

The most recent epidemic of any magnitude in Ireland occurred in 1907, when certain Irish cities—Dublin, Cork, Belfast—suffered simultaneously with certain towns in Scotland, especially Glasgow, Edinburgh, Leith, Grangemouth, and Falkirk.

In England and Wales, records of visitations during the first half of the nineteenth century are very scarce, and there was certainly no epidemic prevalence. It was the severe epidemic in the Province of Dantzig in 1865, an account of which was presented to the Epidemiological Society of London by Hirsch, that was the means of directing the attention of the profession to the disease in this country. From Rochester several cases were reported in 1865 by Brown (1865), and small groups of cases occurred in Birmingham, Bath, Plymouth, and Oxford. In 1885-86 a typical outbreak was reported among the garrison at Devonport, and also among the men in the warships at the harbour. Since that time, although nothing in the shape of an extensive epidemic has occurred in England, there have been numerous small groups of cases in various English counties, a summary of which will be found in Bruce Low's paper.

From 1877 to 1886 the average yearly mortality from the disease in England and Wales was only 40·6, according to the certified returns, and from 1887 to 1896 only 23·3 (population of England and Wales in 1891, 29,002,525). It is highly probable, however, that these figures do not represent the total number of deaths from this cause, as, owing to the difficulty of recognition, genuine cases may well have been classed under such categories as inflammation of the brain, tubercular meningitis, idiopathic tetanus, influenza, etc. In the useful map of England and Wales which accompanies Bruce Low's memoir, one can recognize at a glance the counties in which the prevalence has been most marked. These were for the period 1886-1896: Cheshire (2·21 deaths per 100,000 population), Cumberland (1·12), Stafford (1·53), Lincoln (1·28), Norfolk (1·08), Suffolk (1·41), Herts (1·38), Gloucester (1·46), Monmouth (1·81), North Wales (1·11), Devon (2·20), Cornwall (1·88), and Somerset (1·57). Counties in which the prevalence was under 0·75 per 100,000 were Westmoreland, North Riding of Yorkshire, Derby, Shropshire, South Wales, Hereford, and Worcester.

On p. 230 are tabulated the deaths which occurred from cerebrospinal fever during the period 1897 to 1909 (extracted from Report of Registrar-General for England and Wales).

Of the 130 deaths from cerebrospinal fever in 1909, 35 occurred in London, 30 in Lancashire, 14 in Northumberland, 12 in Glamorgan, 5 in Surrey, and 5 in the West Riding. In other counties there were either 3, 2, 1, or none. In 1910 the deaths from this cause in London rose to 133. Owing to the difficulty of diagnosis, particularly in sporadic outbreaks, we must accept these official mortality returns with reserve. As notification becomes more general, and bacteriological aid in diagnosis more widely employed, it will be possible to form a more correct estimate of the mortality from cerebrospinal meningitis following infection by the meningococcus of Weichselbaum.

In Scotland no cases of cerebrospinal meningitis were reported as such up to 1884, when Dr. Frew drew attention to the occurrence of a group of cases in his own practice in Ayrshire. In 1896 the same observer, at a meeting of the British Medical Association at Carlisle, stated that he had collected notes of over 100 cases of cerebrospinal meningitis that had occurred in Scotland. In the light of Dr. Frew's belief that where a disease is not expected it is not looked for, it is of some interest that in Scotland during the period 1883-1895 the average yearly number of deaths certified as due to cerebrospinal meningitis was only 5·6, while under the heading "Inflammation of Brain" an average of no fewer than 1,568 deaths was certified.

Year.	Total Number of Deaths at all Ages from Cerebrospinal Fever in England and Wales.	Per Million Living Persons.
1897	10	0
1898	11	0
1899	21	1
1900	9	0
1901	59	2
1902	60	2
1903	68	2
1904	81	2
1905	127	4
1906	71	2
1907	161	5
1908	116	3
1909	130	4

In 1906-1908, the disease appeared in epidemic form in Scotland, the chief centres of attack being the large seaport towns on the Firth of Forth and the Firth of Clyde (Glasgow, Edinburgh, Greenock, Leith, Dundee, Paisley, etc.). For an account of this, the most recent epidemic in Great Britain, and the simultaneous epidemic in Ireland, the reader may be referred to reports by Ker (1908), Robertson (1907), Robb (1907-08), and other observers of the time.

The following figures, extracted from the Report of the Registrar-General for Scotland, show the rise and gradual decline of the epidemic which broke out in Scotland in 1906:

	Number of Deaths from Cerebrospinal Fever.
1905	2
1906	301
1907	1,732
1908	445
1909	154

The death-rate from cerebrospinal fever in 1909 was 3 per 100,000 persons living; in 1908, 9 per 100,000; and in 1907, 38 per 100,000.

Of the 154 deaths in 1909, 48 occurred in Glasgow, 16 in Edinburgh, and 10 in Aberdeen. They were thus distributed according to districts:

	Deaths from Cerebrospinal Fever.
Principal town districts (total deaths, 35,561)	95
Large town districts (total deaths, 9,696)	23
Small town districts (total deaths, 14,112)	20
Mainland rural districts (total deaths, 13,595)	16
Total	154

121 of these 154 deaths were of children under fifteen years of age.

In Ireland only 14 deaths from this cause occurred in 1910. In 1909 there were 46, and in 1908, 127.

THE MAIN FEATURES OF CEREBROSPINAL OUTBREAKS.

Wherever cerebrospinal meningitis has broken out it has almost invariably presented certain characteristic features, some of which find a tolerably adequate explanation in the results of recent bacteriological investigations carried out from the "carrier" point of view, especially those of the past seven years, dating from the great outbreak in Silesia, 1904-05.

The most striking feature has always been its sudden and apparently inexplicable appearance in localities hitherto exempt from invasion. The localities affected in a certain area have often been widely separated, while the intervening districts and often the immediate neighbourhood of the affected spots have remained untouched. In such cases the immunity has lasted not merely during the course of the epidemic in the affected centres, but after it has died down in these centres.

Where considerable areas have been overrun, the extension has taken place, as Hirsch remarks, not in a continuous fashion or along radial lines, but in an irregular manner, and as it were *per saltum*. A notable exception to this rule was the mode of spread of the military outbreaks in France during the first half of the last century. The disease appeared to follow very closely the movements of the troops from place to place, and it was only in a very few instances that infection extended to the surrounding civil population. According to Hirsch, of 62 epidemics in France, the malady in 43 cases was absolutely confined to the soldiery of the place, in 6 it was chiefly among the troops, and only occasionally among the tradespeople, and in 5 it was equally common among civil and military. Not infrequently, also, the epidemic was confined to one particular regiment or division in a large barracks. Thus, at Versailles, in the epidemic of 1839, 116 cases out of a total of 160 occurred in the 18th Regiment of Infantry, the rest being distributed over four other infantry regiments and three divisions of cavalry. Another interesting fact with regard to these military outbreaks was that officers or bandsmen who had their homes outside the affected barracks escaped attack. We shall see in the next chapter that the investigations into the frequency of healthy carriers in connection with military outbreaks throw not a little light on the mode of spread in these cases.

The limitation of the disease to certain classes of the population has been a feature of many outbreaks outside military populations. Thus, one may cite the outbreaks in Irish workhouses in 1846, the outbreaks in Indian gaols, American convict prisons, Vienna orphanage, etc. In more recent times outbreaks among the military resident in barracks have been much less frequent, and there can be little doubt that the one factor common to all such institutional outbreaks and to the extensive outbreaks in densely populated districts has been overcrowding and unhealthy sanitary conditions. It has frequently been noted by the more recent observers that the lower classes of the population, living in unhealthy surroundings and in overcrowded tenements, have suffered most severely in times of epidemic. Another feature of these epidemics is their almost invariable occurrence during the winter and spring months. Commencing in the winter months, they reach their acme in the early spring, and then slowly recede during the summer months to disappear almost entirely with the commencement of autumn. The figures for the incidence of cerebrospinal meningitis in Prussia during the years 1904-1907 may be adduced in illustration :

	1904.	1905.	1906.	1907.
January	11	139	216	149
February	11	320	313	260
March	11	759	370	362
April	14	1,010	403	467
May	8	776	258	425
June	9	339	122	301
July	5	124	85	154
August	9	72	51	122
September	5	44	43	102
October	3	47	61	120
November	17	60	56	64
December	15	72	51	57

It has been noticed also in tropical areas that outbreaks of cerebrospinal meningitis occur at that period of the year when dry winds prevail and catarrhal conditions of the throat are frequent—*e.g.*, Jaffé's accounts of the epidemic in the German Protectorate of Togo (1909).

Finally, we may note as one of the most important features of cerebrospinal meningitis, its excessive incidence on young children under the age of fifteen. The percentages of incidence on various age-groups vary somewhat in different epidemics, but it may be said that fully 80 to 90 per cent. of the attacked are children under the age of fifteen. One may quote here the figures from the German Health Reports for the years 1905-1907 :

Age Group.	1905.	1906.	1907.
0 to 1	298	151	333
1 ,, 2	285	148	239
2 ,, 3	333	159	243
4 ,, 5	673	320	450
6 ,, 10	982	536	514
11 ,, 15	425	248	286
16 ,, 20	281	213	219
21 ,, 25	102	107	113
26 ,, 30	53	40	61
31 ,, 40	69	55	76
41 ,, 50	44	32	38
51 ,, 60	24	15	19
61 ,, 70	6	3	4
71 ,, 80 (unknown) ..	186	11	—

It will be seen that out of 3,578 cases of all ages (omitting 186 whose ages were not ascertained), 2,996, or 83·7 per cent., were children under the age of fifteen in 1905. In 1906 and 1907 the percentages were 76·98 per cent. and 79·7 per cent. respectively. In the military epidemics it has been pointed out by Hirsch and others that the soldiers affected were mostly young recruits between the ages of eighteen and twenty-four.

The mortality in the more recent epidemics has been uniformly high. Thus, in the epidemic of 1905 in Upper Silesia the mortality was 67 per cent. ; in America, of 4,000 cases in recent years, 73·5 per cent. proved fatal ; in Belfast, in 1907, of 230 cases, 70·43 per cent. proved fatal (Robb) ; and in the epidemic in Scotland similar figures were reached. Since the introduction of serum therapy, however, numerous observers have notified a reduction in the mortality from 70 to 20 per cent. and under (Flexner, 1912). In the following section we shall deal with the data on the carrier question gathered from various sources.

II. THE OCCURRENCE OF THE MENINGOCOCCUS IN PATIENTS AND CARRIERS.

The specific cause of cerebrospinal meningitis was discovered by Weichselbaum in 1887 to be a Gram-negative diplococcus, to which he gave the name of *Diplococcus intracellularis meningitidis*, and it is of some importance to note that the 6 cases in which he was able to demonstrate this coccus were sporadic cases in Vienna, there being at the time no epidemic prevalence of the disease. Weichselbaum's observations gradually received general acceptance, and more particularly at the hands of Councilman, Mallory and Wright (1898) in America, Faber (1900) in Copenhagen, Bettencourt and França (1904) in Portugal, and especially of Weichselbaum's own pupils, Albrecht and Ghon (1901), who had an opportunity of investigating the disease in its epidemic form at Trifail in Steiermark, where 200 cases occurred. The controversy which arose over the published statements of Jaeger (1895) regarding the presence of a coccus of varying Gram-fastness in the Stuttgart epidemic of 1893 must now be regarded as of historical interest merely, Jaeger's observations on this point having received little or no confirmation at the hands of subsequent workers.

It is now generally accepted that the meningococcus of Weichselbaum is the sole cause of cerebrospinal meningitis, both in its sporadic and epidemic forms. It is with the latter form that we shall be mainly concerned in this section. Later, some reference will be made to the sporadic and so-called postbasic types of cerebrospinal meningitis, when we shall find that bacteriological research of recent years has revealed the presence of organisms other than the meningococcus in certain isolated cases presenting clinical symptoms similar to those following infection by the meningococcus. Before proceeding to discuss the data relating to the distribution of the meningococcus in the organs of actual cases and carriers, it may not be amiss to summarize in brief terms the methods of isolation and criteria of identification which are in vogue at the present day. The methods of identification employed by the earlier workers have undoubtedly to be taken into consideration in forming an estimate of the reliability of the statistics collected by them, but as it is obvious that there can be no actual measure of their reliability, we are under the necessity of giving these authors the benefit of the doubt in those cases where, for example, a particular identification test, now considered indispensable, was not applied.

Methods of Isolation and Identification.

Material from Naso-Pharynx.

Material from the naso-pharynx is taken by means of a swab fixed to the end of a bent rod which is passed in through the mouth. The swab containing the material should be, either immediately or as soon as possible after removal, rubbed over the surface of a plate containing ascitic or serum agar with glucose and litmus, or inspissated serum with glucose and neutral red (as suggested by Buchanan, 1907). The colonies of the meningococcus will then appear red on the medium. The red colonies are picked off, and if proved to be Gram-negative are subplanted on certain fluid carbohydrate media containing a little ascitic fluid. The meningococcus produces an acid reaction in media containing glucose and maltose, but not in media containing cane-sugar, lævulose, or lactose. The following table shows the reactions on these sugars of the meningococcus and other Gram-negative organisms :

	Glucose	Maltose.	Cane-Sugar.	Lævulose.
Meningococcus	+	+	—	—
Gonococcus	+	—	—	—
Micrococcus catarrhalis ..	—	—	—	—

Occasionally Gram-negative organisms are met with in the throat which are easily distinguishable by their power of fermenting saccharose. Differentiation from the gonococcus does not, except in rare cases, come into consideration, and it has to be noted that the action of the meningococcus on maltose is not invariable, while some strains of gonococcus are able to ferment maltose. Subcultures should also be made on serum agar and incubated both at 37° C. and at 22° C. At the latter temperature the meningococcus is unable to grow.

A meningococcus growth is readily emulsified in saline, and only rarely agglutinates spontaneously. On the other hand, the *Micrococcus catarrhalis* always agglutinates spontaneously in saline, and the gonococcus forms as a rule a bad emulsion.

By means of a powerful polyvalent antimeningococcal serum an agglutination test may be applied to the suspected culture, but it has been shown that such agglutination tests are of value only when a positive reaction (1 in 200 to 1 in 1,000) is obtained with the specific serum used. Controls with normal serum should always be put up. Some strains are agglutinated only by the homologous antiserum, but it would appear that strains derived from the same epidemic are agglutinated by a serum prepared by immunization with one of their number.

The greatest difficulty is experienced in differentiating the meningococcus from the gonococcus. Serological tests have up to the present failed to afford satisfactory criteria for the differentiation (Arkwright, 1911) of these two organisms. When the necessity for such differentiation arises, the chief points to which attention has to be directed are the nature of the growth on serum agar and its emulsibility in saline. On serum agar the gonococcus is scarcely visible in twenty-four hours, and the colonies are never confluent as in the case of the meningococcus. Further, as we have already noted, the gonococcus does not readily emulsify in saline.

DISTRIBUTION OF THE MENINGOCOCCUS IN PATIENTS AND CARRIERS.

With regard to the distribution of the meningococcus in the organism generally it is sufficient here to note that in addition to the meningeal exudates of the brain and spinal cord and the naso-pharynx it has frequently been found in the blood, spleen, pleural and pericardial exudates, and other situations ; but the sites that concern us chiefly from the epidemiological and pathogenetic points of view are the naso-pharynx and the blood-stream.

Examination of the Naso-Pharynx in Cases of Meningitis.

The first to identify the meningococcus by cultural methods in the nasal passages of meningitis cases were Albrecht and Ghon (1901) in the course of their investigation of the epidemic at Trifail. These authors examined fifteen persons who had either recovered from the disease or who had been in intimate association with patients. In most of the cases they observed Gram-negative cocci microscopically, but only in one case were the organisms identified by their cultural properties as genuine meningococci.

Similar observations have been numerous since that time, and it is now possible to give some idea as to the frequency with which the organisms are met with in this situation, and their period of survival after the infection has passed off. The material which formed the basis of the pioneer systematic investigations into the occurrence of meningococci in the naso-pharynx of meningitis cases came mainly from the great Silesian epidemic of 1904-05. This was worked out on its bacteriological side by many observers, and notably by von Lingelsheim (1906), of the Beuthen Institute in Upper Silesia.

Data of von Lingelsheim.—Von Lingelsheim examined the nasal and throat secretions in 786 cases of meningitis, and demonstrated the presence of meningococci in 182 cases—*i.e.*, in 23·12 per cent. The following table gives the results he obtained with samples received at different periods of the disease :

Day of the Disease.	Negative Cases.	Positive Cases.
1st to 5th day	233	147—*i.e.*, 38·67 per cent. of total.
6th ,, 10th ,, ..	122	22 ,, 15.2 ,, ,,
11th ,, 20th ,, ..	102	7 ,, 6·4 ,, ,,
After 21st day	147	6 ,, 3·9 ,, ,,
Totals	182	604

All these samples, however, were not of like origin. Only about 50 per cent. of them came from the town and district of Beuthen, and were therefore received for examination on the day of their withdrawal from the patient. With these—390 in number—a higher percentage of positive results was obtained, as might be expected from one's knowledge of the brief extracorporeal period of survival of the meningococcus; 130, or 33·3 per cent., of this total were positive, and these may be arranged according to the period of the disease at which they were taken, thus :

Day of the Disease.	Total Received.	Positive.	Percentage of Positive Results.
1st to 5th day ..	156	104	66·60 per cent.
6th ,, 10th ,, ..	57	14	24·56 ,,
11th ,, 20th ,, ..	62	7	11·29 ,,
After 21st day ..	115	5	4·39 ,,

A still higher percentage was obtained in a series of 60 cases treated in the hospital at Beuthen—viz., 70·6 per cent.—and in a later paper von Lingelsheim (1908) states that these 46 positive results referred to a series of 49 patients whose naso-pharynx secretions were examined in the early stage of the disease. This would give the very high percentage of 93·8 per cent. for the frequency of the meningococcus in the naso-pharynx at the outset of the disease. Samples received from more remote districts gave, on the other hand, percentages as low as 16·1 and 8·8 per cent. Von Lingelsheim's conclusion was that after three weeks over 90 per cent. of all cases of meningitis would be free of meningococci in the throat and nasal passages.

Data of Goodwin and von Sholly.—A small series of cases investigated by Goodwin and von Sholly (1908) in America yielded results very similar to those of von Lingelsheim. Only fifty-two cases were examined at different periods of the disease, with the following positive findings in the naso-pharynx :

Week of the Disease.	Number of Cases.	Positive Results.	Percentage of Total.
1st week	22	12	54·5 per cent.
2nd ,, ...	15	5	33·3 ,,
3rd ,, ...	6	—	—
4th ,, ...	3	—	—
5th to 9th week ..	6	—	—
67th day	1	1	—

It seems probable that if cases came under observation at a sufficiently early period the naso-pharyngeal secretions would invariably be found to harbour the meningococcus. Thus, a small but well-observed series by Herford (1908) in Altona yielded positive results in all the cases examined during the early days of the disease :

Period of Disease.	Number of Cases.	Positive.	Percentage of Total.
2nd to 8th day	11	11	100 per cent.
14th day or later ..	6	—	—

Herford, in fact, strongly recommends this method for diagnostic purposes, and gives illustrations of its successful employment in cases where lumbar puncture was not permitted.

In the acute stage of the disease Debré (1911) had 11 positive results out of 15—*i.e.*, 73·3 per cent.

Period of Survival of the Meningococci in the Throats of Convalescents.

From the above statistics, and others not quoted here, it would appear that in the great majority of cases the meningococci disappear from the naso-pharynx after the third week. None the less, some very marked instances of chronic carriage of the meningococcus have been observed after convalescence. Thus, we may note the case reported by Goodwin and von Sholly, in which the cocci were recovered from the naso-pharynx nine weeks after the commencement of the disease ; also a similar case by Herford, in which the cocci were still present two months after the beginning of the infection. Debré (1911) made repeated examinations of thirteen cases more than three weeks after recovery, but in two cases only was he able to recover the meningococcus from the naso-pharynx—viz., one on the forty-third day, and one on the eightieth day after the onset of the disease.

So far we have no data dealing with the examination of convalescents for prolonged periods after recovery, so that we are not in a position to say what proportion of convalescents become chronic carriers. Such examinations would require to be continuous, as objection has been taken to the genuineness of these long periods of carriage on the ground that a reinfection might readily have taken place.

HEALTHY CARRIERS OF THE MENINGOCOCCUS.

We come now to discuss the so-called healthy carriers of the meningococcus, and these it will be convenient to classify into two groups :

1. Those who have lived more or less in the vicinity of meningitis cases. This group includes also those in whom the carrier state has been accompanied or preceded by symptoms suggesting an abortive meningococcal infection.
2. Those who have not obviously been associated with cases of meningitis—at least, in its epidemic form.

Group I. : Carriers in the Neighbourhood of Meningitis Cases.

Kiefer's (1896) demonstration of the meningococcus in his own throat deserves to be mentioned first, as it was the earliest instance of the finding of meningococci in the throat of an apparently healthy person. He had been working in the laboratory with cultures of the meningococcus, and in the course of his work contracted a severe rhinitis, from the discharge of which he was able to isolate and definitely identify the meningococcus of Weichselbaum. Naturally, some doubt may be felt on the question whether the rhinitis was of specific meningococcal origin, and, if so, whether the infection actually proceeded from the artificial cultures.

The first systematic investigation into the question was made by Albrecht and Ghon (1901) in the course of the Trifail epidemic.

The throats of fifteen healthy persons who had frequently been in contact with cases of the disease were examined.

In most of the cases Gram-negative diplococci were to be seen microscopically, but in one case only was a culture obtained and identified. This was from a man whose child had died on the previous day of meningitis.

Data of von Lingelsheim.—The Silesian epidemic of 1904-05 gave rise to extensive investigations of this kind. Material from various districts in the epidemic area was examined and reported on by von Lingelsheim (1906), the contacts being intimate relations—parents, brothers, sisters—of the cases. The results obtained varied according to the district, and appeared to depend to some extent on the time taken for the specimen to reach the bacteriological laboratory. In three districts the percentages of positive contacts were 11, 16·6, and 7·14 per cent., with an average carrier frequency of 15 per cent.

Data of Buchanan.—During the epidemic in Glasgow (1907), Buchanan went into the question of contact carriers; 308 contacts in 74 families were examined, with 81 positive results, giving a carrier frequency of 26·3 per cent. These 81 positive contacts belonged to 51 families, so that the percentage of families containing one or more carriers was 68·9 per cent. A further analysis of the data yielded the following interesting facts:

The 51 positive families were arranged thus, according to the number of carriers found in each:

Number of Families.	Number of Carrier Members.	Total.
31	1	31
14	2	28
3	3	9
2	4	8
1	5	5
Total 51		81

As we shall see later, Trautmann (1908) lays stress on the great importance of carrier families in which practically all members are found to be carriers, but it will be seen that Buchanan's figures lend no support to the contention that such carrier families yield the great majority of positive contacts in an infected population. Some further points of interest emerge on analysis of Buchanan's figures. In the first place, with regard to age, the 81 carriers may be arranged thus:

Age.	Number of Carriers.	Age.	Number of Carriers.
Under 1 year	1	15 to 20 years	12
1 to 5 years	9	20 ,, 30 ,,	10
5 ,, 10 ,,	12	30 ,, 40 ,,	15
10 ,, 15 ,,	8	40 ,, 50 ,,	11
		50 ,, 60 ,,	2
		60 ,, 65 ,,	1
Total ..	30	Total ..	51

Showing that persons above school age (over fifteen years of age) form the great majority of the contact carriers.

Secondly, the carriers may be arranged according to their position in the respective families thus:

Position in Family.	Number.
Fathers	17
Mothers	15
Sons	24
Daughters	11
Uncle	1
Grandfather	1
Grandmother	1
Lodgers	7
Visitors	4
Total	81

Data of Bruns and Hohn (1908).—Bruns and Hohn have reported on a most extensive series of examinations of nasopharyngeal swabs taken during the course of the epidemic in the coal-mining district at Gelsenkirchen (March to August, 1907).

During that period the following notifications of cerebrospinal meningitis were made:

March	148	including	16	suspicious cases.
April	278	,,	14	,, ,,
May	327	,,	25	,, ,,
June	188	,,	0	,, ,,
July	146	,,	1	,, ,,
August	68	,,	24	,, ,,
Total	1,155		80	

For the same period the number of swabs sent for examination from contacts among the suspected population and the number of positive results obtained were as follows:

Month.	Number of Examinations.	Number of Positive Results.	Percentage of Positive Results.
March	120	37	30·1 per cent.
April	641	152	23·7 ,,
May	730	113	15·5 ,,
June	644	88	12·1 ,,
July	616	53	8·6 ,,
August	403	22	5·5 ,,
Totals	3,154	465 = 14·7 per cent.	

These samples, however, did not all reach the Institute at the same interval after removal from the patient. Some were taken by the authors themselves or in their presence, and immediately plated; others arrived by messenger; while others, again, came by post after an interval of twenty-four to forty-eight hours.

By grouping these according to the way in which they reached the Institute, one can see clearly the effect of long transit on the viability of the meningococcus.

Samples taken by the authors	593,	of which	192,	or	32·4	per cent.,	were positive.
Samples brought by messenger	1,193	,,	209	,,	17·5	,,	,,
Samples received by post within 24 hours	1,324	,,	63	,,	4·7	,,	,,
Samples received by post within 48 hours	20	,,	0				
	3,130	,,	464	,,		,,	,,

If we exclude the samples which came by post—viz., 1,344—there remain 1,786 samples, which may be grouped thus:

March	56	swabs,	of which	34,	or	60·7	per cent.,	were positive
April	360	,,	,,	116	,,	32·2	,,	,,
May	408	,,	,,	97	,,	23·8	,,	,,
June	352	,,	,,	84	,,	23·9	,,	,,
July	323	,,	,,	49	,,	15·1	,,	,,
August	287	,,	,,	21	,,	7·3	,,	,,
Total	1,786	,,	,,	401	,,	22·5	,,	,,

A comparison of these figures with those for the number of clinical cases of the disease occurring during these months shows fairly clearly that during the rise and height of the epidemic the percentage of successful inoculations from healthy contacts was much higher than during the fall of the epidemic. To this interesting result, and the speculations to which it gives rise, we shall have occasion to refer in a later section.

In the light of Buchanan's figures, it is of interest to compare the analysis of Bruns and Hohn's data for the frequency of carriers in families in which a case of meningitis occurred :

Month.	Number of Families Examined.	Number of Families containing Carriers in addition to Cases.	Number of Families containing Cases but no Carrier.	Number of Members in Families.	Percentage of Positive Cases.
March ..	7	7	—	23	14 = 61 per cent.
April ..	39	37	2	135	67 = 50 ,,
May ..	43	40	3	172	81 = 47 ,,
June ..	23	18	5	93	34 = 36·6 ,,
July ..	21	11	10	67	18 = 27 ,,
August ..	22	7	15	119	10 = 8·5 ,,
Totals ..	155	120	35	609	224 = 36·7 ,,

Thus, during the rise of the epidemic (March-May), 84 of the 89 families contained one or more carriers, whereas during the fall of the epidemic (June-August) only 36 of the 66 families contained carriers. In these 89 families there were 330 members, and 162 of these (or nearly 50 per cent.) were carriers ; while in the 66 families examined during June-August, and containing 279 members, only 62, or 22·2 per cent., were carriers.

If we take the totals for the whole epidemic, we find that 609 contacts in 155 families were examined, of whom 224, or 36·7 per cent., were positive (compare Buchanan's figure of 26·3 per cent.).

These carriers belonged to 120 families, so that the percentage of positive families to the total examined was 77·4 per cent. (compare Buchanan's figure of 68·9 per cent.). The analysis of Bruns and Hohn's data according to the position of the carriers in the family is also of interest in the light of Buchanan's similar analysis:

Month.	Fathers.		Mothers.		Brothers and Sisters.		Other Inmates.	
	Total Examined.	Positive.	Total Examined.	Positive.	Total Examined.	Positive.	Total Examined.	Positive.
March ..	7	3	2	2	14	9	—	—
April ..	28	17	20	12	76	34	11	4
May ..	31	19	34	11	97	49	10	2
June ..	21	11	17	7	55	16	—	—
July ..	15	7	19	6	33	5	—	—
August	11	3	22	1	85	5	1	1
Totals ..	113	60	114	39	360	118	22	7

Here also it would appear that a higher percentage of the fathers and mothers are likely to be carriers than of the brothers and sisters of the affected member. Bruns and Hohn, in fact, are inclined to suggest that it is through the fathers in the first instance that infection is conveyed to the family.

Some interesting observations on the frequency of carriers in military units, and the rapidity with which a case becomes surrounded by an ever-widening ring of carriers, have been made by Bochalli (1908), Dieudonné (1906), and Hasslauer (1906). Bochalli's material came from an epidemic among the military in Upper Silesia. Up to April, 1906, there had been 28 cases of the fever, with 16 deaths, in the Sixth Army Corps. Two cases occurred in March, 1906, the latter on the 20th. On the 28th—*i.e.*, eight days after the commencement of his illness—the room-mates of the 6 cases which had been isolated were examined, and out of 16, 10 were found to be carriers. Of 10 soldiers in the adjacent dormitory, 3 were positive, and 3 carriers were found also in two other dormitories.

Altogether 41 persons were examined with 16 positive results, —*i.e.*, 39 per cent. It is of interest that 4 of these carriers were drafted to hospital suffering from suspicious symptoms—headache, neck pains, etc.—but these cleared up rapidly, and the cases were discharged. The symptoms were attributable to a pharyngitis which may very possibly have been of meningococcal origin. In a later chapter we shall enter more fully into the question of the so-called pharyngitis in meningococcal carriers.

After concluding these investigations in the immediate entourage of the cases, Bochalli proceeded to examine the whole battalion. Thirty men were examined daily, and the cultures obtained were fully proved by fermentation and agglutination tests. Of 485 men examined, 42 were found to be carriers—*i.e.*, 8·6 per cent.—and they were grouped thus according to their companies :

9th Company	..	130 examined	..	23 positive.
10th ,,	..	123 ,,	..	9 ,,
11th ,,	..	122 ,,	..	8 ,,
12th ,,	..	110 ,,	..	2 ,,
Total ..	..	485	..	42

By grouping these cases in such a way as to show up the percentages amongst units of greater or less remoteness from the actual cases, very striking results were obtained. Thus, of the

16 room-mates of the case, 10 were positive, as mentioned—*i.e.*, 62·5 per cent.

The 9th Company, containing 114 men (130 – 16), and which might be considered the next stage of remoteness, gave a carrier percentage of 11·4 per cent. The other three companies had no direct relation to the cases, and it will be seen that of the 355 men in them, only 19 were carriers—*i.e.*, 5·4 per cent. The farther one went from the immediate neighbourhood of the cases, therefore, the less was the chance of finding carriers.

Dieudonné (1906), like Bochalli, investigated a small outbreak in the Bavarian 1st Train Battalion. Twenty-nine soldiers were isolated as suspects with symptoms of throat catarrh. Four of them were found to be carriers, but none developed the disease later. Further, all the men (39) of a room in which several cases had occurred were examined, and 5 carriers were discovered. These carriers had slept in beds adjacent to 2 of the attacked soldiers.

Dieudonné notes that one of the carriers took ill two days after the naso-pharynx was examined with symptoms of headache and vomiting. No more serious symptoms supervened, however. Also, two of the carriers had severe nasal and throat catarrh, while the remaining two presented no disturbance of any kind.

Hasslauer (1906) also investigated a small epidemic of 7 cases in a battalion. The contacts examined were 89 soldiers, either healthy or suffering from other diseases, but who had come into relationship with cases of meningitis. Nine of them were found to be carriers—viz., 10 per cent.

A similar percentage was obtained by Goodwin and von Sholly (*loc. cit.*) from a series of 45 healthy persons living in close contact with meningitis patients, 5 carriers being discovered. The examination of the contacts took place during the first two weeks of the patients' illness.

Ostermann (1906) (Silesian epidemic) confined his attention to families in which the children had contracted the disease. Six such families were investigated, the specimens being taken by the author himself from the various contacts, and plated within four and a half hours of the taking of the samples. Unfortunately, Ostermann does not state what time had elapsed between the onset of a case and the investigation of the contacts in the particular family. As will be apparent from recent work on the subject of carrier contacts, this is a point of great importance for a correct appreciation of the frequency of carriers in the neighbourhood of freshly occurring cases.

In each of the 6 families Ostermann discovered carriers—viz., 17 out of a total of 24 possible family contacts (*i.e.*, 70 per cent.). He also examined the children in a school of a district in which a certain family (" K ") had been affected with meningitis. Forty-nine children were negative, but two girls (eight years and ten years respectively) were found positive. These two girls sat in the same class and associated with a girl who belonged to the family " K," and was also a carrier.

The material worked up by Selter (1909) came from an epidemic in Bonn in the beginning of 1909. He confined his attention to the occurrence of carriers in families where meningitis had arisen. These carriers were carefully investigated, repeated examinations being made. Space will permit of a description of the steps taken in one only of these families.

On January 31 a girl (" G "), aged thirteen years, was brought to hospital, where a diagnosis of cerebrospinal fever was confirmed by lumbar puncture. Three days later the mother also took ill. The members of the affected family, and also the families which had intercourse with them, and worked in the same factory, were brought to the Institute, and it was decided in the first instance to isolate the members of the family " G," and, should carriers in other families be found, to isolate them also, the town supplying the necessary funds, and the director of the factory guaranteeing full pay during the period of detention. Of the 26 persons examined, 8 were found to be carriers. Two of them belonged to the family " G," while 6 belonged to other families. On February 6, 4 other families with 12 persons were isolated, and 1 was found to be carrying on February 7. The carriers in the family " G " were the father and the eldest daughter. Both these cases continued to harbour the cocci over four months.

Thus, in the mother " G," positive results were obtained on February 3, March 5, March 12, March 19, March 25, April 4, April 15, May 2, June 4. One negative result was obtained on April 13. The girl " G " gave positive results on February 3, March 25, April 4, April 7, April 15, and June 4.

The father " G," one of the healthy carrier contacts, gave positive results over a long period—viz., May 2, June 4, July 8, —and as this person and his daughter were engaged in the factory, it was determined to ascertain whether any of the persons associated with them in the works were carriers. Accordingly, on July 28, 25 of them were examined, with 7 positive results. On August 28 these carriers were all examined again, and in 4 of them, including father "G," the meningococci were still present. Thus, the father had carried the cocci almost seven months. Similar prolonged carriage of the meningococcus was observed in members of the carrier families. Thus, in one case the family was kept under isolation for seven weeks. During that time samples were taken from all the members at intervals of five or seven days. It was noted in one case that, although two members only—viz., the mother and an infant—were carriers on the first day of isolation, the whole family of six had become carriers within ten days. Occasionally one member remained free of the cocci throughout the whole period, while others began to harbour them only at a late period. These detailed observations by Selter form the best material for estimating the period of viability of the meningococcus in the throats of healthy carriers, and the rapidity with which carriers multiply.

The following investigation, showing how one carrier gradually becomes surrounded by a zone of carriers, is recorded by Selter. On October 6 a recruit who, three months before, had recovered from meningitis, entered a Hussar regiment in Bonn.

On October 9 the fact of his previous illness was ascertained for the first time. Meningococci were found on this date in the naso-pharynx. Next day swabs were taken from eight persons living in the same room with the carrier. Four other carriers were found and isolated.

On October 13, 30 men living on the same floor were examined, and 10 carriers discovered. On October 19, 30 men of the underfloor (older soldiers) were examined, and 6 carriers discovered. All carriers were isolated. As a control series, 27 men of an infantry battalion were examined, and 2 carriers were discovered. No connection could be found between these and patients or carriers. These last carriers were not isolated.

During the period February, 1907, to April, 1908, cases of cerebrospinal meningitis to the number of forty-eight occurred in Altona, and Herford (1908) took the opportunity of making a number of interesting bacteriological observations on the cases. Here we are concerned merely with the data he established on the frequency of contact carriers. During the fourteen months he examined 192 healthy people living in 33 families, and found 46 carriers—*i.e.*, 23·9 per cent. These carriers belonged to 24 families (72·7 per cent. positive families). The examinations were made after notification of a case in a family, the material from the throat being plated immediately in the patient's house.

Trautmann (1908) and Trautmann and Fromme (1908) were also making observations at the same time in connection with the cerebrospinal cases in the neighbouring city of Hamburg, where 100 cases occurred.

In all, 227 people belonging to 68 families were examined, and 22 carriers were discovered—*i.e.*, 9·7 per cent.

Also, they discovered 2 carriers out of 34 individuals not living in families. Thus, 24 carriers in all were discovered out of 261 persons examined—viz., 9·1 per cent. (Herford's figure for Altona was much higher—23·9 per cent.).

The plates were made within two hours after the swabs were taken from the case. Trautmann lays particular stress on the fact that a very large proportion of the families revealed no carriers, and that, in fact, a few carrier families, in which practically all the members were carriers, formed the majority of the total crop of carriers.

It is of interest to analyse his data more carefully.

Of the 68 families examined, 13 contained a carrier or carriers—*i.e.*, 19·1 per cent. These 13 positive families may be arranged thus, according to the number of positive members found in them.

Number.	Number in Family.	Number Positive.
A	4	4
B	2	2
C	4	4
D	4	3
E	3	1
F	3	1
G	4	1
H	4	1
I	5	1
J	3	1
K	5	1
L	3	1
M	1	1

Thus, three families supplied about half of the total yield of carriers. Where only one carrier occurred in a family, he was generally a young person; but in the carrier families father, mother, and children, were alike attacked, and all continued to harbour the cocci for a long time. He was unable to assign a limit, but certainly up to forty-four to sixty-six days.

Recently Debré (1911) examined the contacts in a series of 20 families, each of which had one of its members a patient. Of 66 contacts in these families, 15 were found to harbour the meningococcus in the naso-pharynx—*i.e.*, 22·7 per cent. Also, in a Paris school attended by about 800 pupils, where an outbreak occurred in March, 1909, 231 children were examined, and 49 of these—*i.e.*, 21·2 per cent.—were found to be carriers.

Finally, Costa (1910) has reported a series of bacteriological investigations among the entourage of cases of cerebrospinal meningitis occurring in various military garrisons in the South of France (Toulon, Marseilles, Antibes, Nice).

First Series.—Among the entourage of an officer: 1 carrier discovered (actual number of persons examined not stated). This carrier was the officer's *brosseur.*

Second Series.—Among the entourage of a soldier: 2 carriers discovered (18 persons examined). These two carriers had slept with the patient during the two nights preceding his admission to hospital.

Third Series.—Among the entourage of a soldier: 5 carriers discovered (26 persons examined). One of these had occupied a bed adjacent to that of the patient.

Fourth Series.—Among the entourage of a soldier: 1 carrier discovered (24 persons examined). This carrier had occupied the neighbouring bed.

Fifth Series.—Among the entourage of a soldier: 8 carriers discovered (24 persons examined). Of these, two were bed-neighbours, and another had lost his wife from cerebrospinal meningitis.

Sixth Series.—Among the entourage of a soldier: 7 carriers discovered (33 persons examined). Of these, two were intimate friends of the patient, and, like the latter, played in the band.

In all, therefore, 24 carriers were discovered out of about 126 possible contacts—*i.e.*, 19 per cent.

Group II.: Carriers not Obviously Associated with Cases of Meningitis.

A large number of such control series have been examined, with varying results, but as a rule the occurrence of carriers in such groups has been very rare. During the Silesian epidemic, von Lingelsheim examined the throats of 184 children suffering from acute inflammatory conditions (scarlet fever, measles, whooping-cough, etc.). All were negative. Negative results were also got by Bochalli (*loc. cit.*), who examined a control series of 40 men belonging to two battalions of the regiment remaining at Gleiwitz, where no cases of meningitis had arisen.

Droba and Kuçera (1906) examined 210 children in an epidemic-free district of Galicia, with negative results.

Ostermann's (*loc. cit.*) results with a small group of persons living certainly in the neighbourhood of affected families, but not in close contact with them, were also negative.

Dieudonné (*loc. cit.*) and Hasslauer (*loc. cit.*), in the case of small groups of men whose regiments were not affected or who had no association with actual cases, had negative results. So also von Lingelsheim (1908), who examined 127 persons who had no relation to cases. Goodwin and von Sholly's investigation of 35 medical students who had never been in contact with meningitis cases gave also negative results.

Only a few observers have been successful in discovering carriers in such groups apart from cases of meningitis.

Thus, Kutscher (1906) made an examination of 56 persons in a Berlin garrison hospital during the winter 1905-06 at a meningitis-free period, and discovered 4 carriers. Also Hübener and Kutscher (1907) examined 400 men of a Berlin regiment in which no cases of meningitis had occurred either before or after, and got 8 carriers—*i.e.*, 2 per cent. of normal soldiers. Selter also examined 35 persons in a throat and nose polyclinic, and got 3 carriers. Kolle and Wassermann (1906) examined 114 persons in Berlin at a time when there was no epidemic prevalence of the disease apart from a few sporadic cases. The persons examined were healthy people connected with the Institut für Infektionskrankheiten, patients in the polyclinic, and in the garrison hospital. In two cases they found meningococci. One was a girl of nine years, who at the time had a stiff neck, and was handed over to the hospital as a suspect. The other was a man whose child was ill with meningitic symptoms, but whether meningococci were later demonstrated in her was not known.

With regard to the occurrence of carriers in populations not obviously related to cases of epidemic meningitis, it is not at all surprising that such should occur when one considers the rapidity with which a healthy carrier can spread infection to remote parts. And, indeed, the occurrence of such cases is necessary to explain the peculiar manner in which cerebrospinal meningitis springs up in areas between which and previously infected areas no apparent connection can be traced.

Period of Survival of the Organisms in the Throats of Carriers.

Bruns and Hohn examined a series of eighty-one healthy carriers from this point of view. In most of them only two to three examinations were made, but in a few the examinations were continued until the examination, repeated at least three times, had given a negative result. In the others, the series closed sometimes with a single negative result, and sometimes with a positive. The figures can therefore be considered only as minimal figures :

	Carriers.
Up to 8 days	28
,, 2 weeks	18
,, 3 ,, ...	13
,, 4 ,, ...	10
,, 5 ,, ...	4
,, 6 ,, ...	3
,, 7 ,, ...	3
,, 8 ,, ...	1
,, 11 ,, ...	1
	81

Apparently, therefore, although in the majority of cases the cocci disappear after two to four weeks, this period may be greatly exceeded in a certain small percentage of carriers. Selter, who made very careful and repeated examinations of his contact carriers during isolation, noted periods of carriage up to seven months. Herford, on the other hand, maintains that there is a class of carrier in whom the cocci persist only a few days (seven to fourteen days in a series of twenty-six healthy carriers). In none of his carriers did he observe a longer period of vegetation than six weeks. It is impossible to supply accurate data on this subject, but there can be no question that in a small percentage of healthy carriers the cocci may remain for a very prolonged and perhaps indefinite period.

III. PATHOGENESIS OF THE CARRIER CONDITION AND DISCUSSION OF THE QUESTION OF DISPOSITION.

There are several questions connected with the pathogenesis of the carrier condition in respect of the meningococcus which lend themselves to discussion, though it must be admitted that our knowledge of the underlying factors is at present somewhat fragmentary.

The principal question that arises is: What are the local or general factors which determine the transitory or chronic vegetation of meningococci in the naso-pharynx of apparently healthy carriers? The answers to this question have been many and varied, and probably the conditions which favour a temporary vegetation differ essentially from those which favour a more prolonged sojourn of the specific cocci.

The first to direct attention to this matter was Westenhoeffer (1905), who, from his work on the pathological anatomy and histology of fatal cases of cerebrospinal meningitis, concluded that inflammatory conditions were invariably to be found in the throats of these cases. In the beginning of the disease, and in acute fulminating cases, Westenhoeffer found an extensive reddening of the naso-pharynx with slimy exudate. Further, the tonsils were invariably enlarged in all cases; the lymphatic glands, not only in the neck, but in other regions of the body (including the mesenteric glands), were swollen and injected, while the Peyer's patches and solitary follicles of the intestine were hyperplastic. All these changes were regarded by Westenhoeffer as lending support to the view propounded by him that, for the development of cerebrospinal meningitis in any particular individual, "lymphatism," or a "status lymphaticus," so called, was an essential predisposing factor. He said: "Die uebertragbare Genickstarre befällt hauptsächlich Menschen mit Lymphatismus." This far-reaching conclusion has by no means received universal acceptation, although Westenhoeffer's work in drawing attention to the inflammatory conditions, particularly in the naso-pharynx, has proved of much service in elucidating the path by which the meningococcus most probably gains entrance to the organism. For a critical estimate of Westenhoeffer's work, one must refer to the experience of subsequent workers, through whose hands large numbers of cases have passed.

Of these, one may quote the experience of Busse (1910), who decided that the majority of cases are accompanied by a more or less severe inflammation of the naso-pharynx, but that there may be great variations. In fulminating cases it was Busse's experience to find only slight reddening of the fauces, whereas in slowly-progressing cases the changes were much more severe. The tonsils were by no means invariably swollen, except, perhaps, in acute cases. Anyhow, all the changes associated with lymphatic hyperplasia were attributed by Busse and most subsequent workers, not to the presence of some underlying lymphatic disposition, but to the pathogenic action of the meningococcus itself.

As might be expected, a large amount of data has been collected in order to test the hypothesis of Westenhoeffer that the lymphatic diathesis is the determining factor in meningococcal infection.

Göppert (1906) examined 130 healthy children and an equal number of children affected with meningitis, with a view to deciding the relative frequency of glandular enlargement in young children (ages six to ten). Both groups were drawn from the same epidemic area, but not from the same confined industrial area. The result of the statistics was that meningitis patients showed much less swelling of the glands than healthy children. He also performed fifty-two autopsies of meningitis cases, paying particular attention to the adenoid vegetations in the naso-pharyngeal wall; but only in three cases did he find any considerable adenoid growth, and these were the only cases in which the removal of adenoids might have been considered as indicated, had the patients come under a physician's care before contracting the disease. Also, in two families he noted that it was the children with most marked disposition to "scrofula" who escaped meningitis. Like Busse later, he found that the fulminating cases did not show so much tendency to glandular enlargement as those of prolonged duration, although such cases often showed swelling of the lymphatic apparatus of the intestine and mesenteric glands. No satisfactory evidence of enlargement or persistence of the thymus gland, as alleged by Westenhoeffer, could be obtained.

The only writer who brought forward evidence which, in his view, does not militate against Westenhoeffer's hypothesis, though not markedly strengthening it, is Meyer (1906). This observer performed rhinopharyngological examinations in a series of cases of meningitis and of healthy children—viz., 100 cases of meningitis, 7 convalescents, 23 healthy brothers and sisters of cases, 70 children in an epidemic area who were kept from school because they lived in the same house with cases, and a class of 52 children belonging to a hamlet which was very little affected by the epidemic. The results of his examination of the pharyngeal tonsils in these cases were as follow :

Pharyngeal Tonsils.	Eighty-seven Patients.	Seven Convalescents.	Healthy.
Normal	32 = 36·79 per cent.	0 = 0·0 per cent.	24·83 per cent.
Slight hyperplasia ..	17 = 19·53 ,,	3 = 42·9 ,,	27·59 ,,
Moderate ,, ..	23 = 26·44 ,,	1 = 14·3 ,,	24·14 ,,
Marked ,, ..	15 = 17·24 ,,	3 = 42·9 ,,	23·45 ,,

Now, Meyer, as Busse has pointed out, employs these figures in a most extraordinary way. He finds that only 18·39 per cent. of all the meningitis cases had normal tonsils in distinction to the healthy children, 24·83 per cent. of whom had normal tonsils. Apparently he gets the former figure by adding 36·79 to 0, and dividing by 2, and similarly he found that 31·22 of the attacked (*i.e.*, 19·53 + 42·9 ÷ 2) had slight hyperplasia, while a smaller percentage (viz., 27·59) of the healthy children presented such. When properly managed, as done by Busse, the 87 patients and 7 convalescents being considered together, the following table is obtained :

Pharyngeal Tonsils.	Cases.	Healthy.
Normal	34·04 per cent.	24·83 per cent.
Slight hyperplasia ..	21·28 ,,	27·59 ,,
Moderate ,, ..	25·53 ,,	24·14 ,,
Marked ,, ..	19·15 ,,	23·45 ,,

Showing clearly that a larger percentage of normal tonsils was to be found in meningitis cases than in healthy children, 75·18 per cent. of the latter showing hyperplastic tonsils, as against 65·96 per cent. of the former. Thus the figures of Meyer, when properly considered, so far from supporting, or at least being not inconsistent with, must be regarded as strongly opposed to Westenhoeffer's thesis.

Another problem which is intimately bound up with the pathogenesis of the carrier state and the disposition to this condition is that of the so-called "meningococcal pharyngitis." During the epidemics of cerebrospinal meningitis, which almost invariably have their acme in the winter and early spring months, it is usual to find a considerable frequency of nasal and pharyngeal catarrh amongst the entourage of meningitis cases, and a large proportion of the carriers revealed in the course of the bacteriological investigations performed under such circumstances have been shown to suffer, in some cases rather severely, from throat troubles. One may cite in this connection the experience of Ostermann and Bochalli, the latter of whom observed twenty-four of his forty-five carriers affected with sore throats, a few of them in a severe form. There is no doubt that certain abortive forms of meningitis may be characterized solely by severe throat symptoms, headache, and herpetic eruptions. Such cases have been noted by Flatten (1909) and others, so that one cannot get away from the fact that in certain persons the meningococcal infection may take on this mild form. Where, however, throat catarrhs are the only evidence of illness, the doubt always arises whether such catarrhs are to be attributed to an actual infection of the throat by the meningococcus which has settled there. On this question opinions have varied, but the prevalent view at the present time is that these affections are directly due to the specific action of the meningococcus. In no other way can one explain the fact that in a certain household—*e.g.*, in which a case of meningitis has occurred—certain members of the family who suffer from throat symptoms, however slight, are found to be harbouring the meningococcus; while in others with perfectly sound throats the specific coccus cannot be demonstrated. Lingelsheim attached little importance to the pharyngitis. He said it could not be proved that the settling of the coccus in the throat led to a pharyngitis, as many carriers of the meningococcus showed no evidence of throat changes. The settling of cocci, in his view, was favoured by the increased mucous secretion present at such seasons as the result of sudden climatic influences (cold, etc.).

Hasslauer also maintains that the subjective symptoms of the so-called "meningococcal rhinitis" are not greater than those following ordinary colds. Two carriers examined by Dieudonné took ill two days after examination of the throat had revealed the presence of cocci, with headache and vomiting, while two others had severe nasal and throat catarrh. Two more had, however, no catarrhal symptoms. Of Bochalli's 43 carriers, 24 had slight or severe pharyngitis, while 19 had normal throats. Also, of 485 men examined, only 281—*i.e.*, 57·9 per cent.—had quite normal throats. Eighteen of these—*i.e.*, 6·4 per cent.—had the cocci in the nose; while of 204 men with slight pharyngitis, 24—*i.e.*, 11·7 per cent.—had cocci. It is certainly difficult to avoid the conclusion that the pharyngitis, when it is present, is the result of the meningococcal infection, or at least that, when precedent to the settling of meningococci, it is aggravated by their action. Flatten, as already mentioned, held that no such proof of infection was forthcoming, and that, in the absence of meningitis symptoms, an infection with the meningococci could not be considered as proven. This extreme view, however, cannot be upheld at the present time, when so much knowledge has accumulated regarding the presence of mild ambulant or abortive forms of infection in other diseases—*e.g.*, enteric fever—and it would seem quite reasonable to draw a parallel between the so-called symptomless forms of typhoid fever and the cases of meningococcal vegetation, which may or may not be accompanied by naso-pharyngeal symptoms. Evidence of infection by the meningococcus from the presence of specific antibodies in the sera of carriers would be of great value, but the available data on this subject are scanty. Such as they are, they go to show that, in a certain proportion of carriers, agglutinins and tropins are demonstrable in the serum. To this question we shall presently allude in detail. Even when we admit that a pharyngitis is to be considered in a large number of carriers as an evidence of meningococcal infection, and may reasonably be regarded as an abortive form of infection, there still remains to be explained the long continuance of the specific cocci in the naso-pharynx after those symptoms have disappeared. Now, according to the data supplied in a previous chapter, the average duration of the cocci in the throats of carriers is probably not less than in actual convalescents, and, as we shall see later, no amount of medication can remove these cocci from their temporary hosts before what one may call their appointed period has elapsed. It would, therefore, appear that the great majority of carriers comport themselves exactly like convalescents who have recovered from the meningeal infection in so far as an infected naso-pharynx is concerned. Although one cannot get away from the idea of a certain disposition to the meningeal invasion which attaches itself mainly to young persons, and for which no satisfactory explanation except a natural susceptibility on the part of young persons can be assigned, one would expect to find that, in at least a certain proportion of carriers who may or may not have presented obvious naso-pharyngeal symptoms, a meningeal invasion would suddenly intervene. As a matter of fact, not a few such invasions have been recorded.

Thus, Bruns and Hohn mention the case of a girl of thirteen who developed meningitis two and a half months after the cocci had been demonstrated in her throat. No examination had been made in the interval, however, and, accordingly, one can conceive that a second infection with a new race of meningococcus may have occurred.

Another girl of eight years developed the disease sixteen days after the first demonstration of the cocci in the throat. Bochalli gives an interesting account of an isolated case of cerebrospinal meningitis which occurred at a sanatorium in Davos. The patient (a female of twenty-five years) arrived at Davos on October 19, 1907, suffering from pulmonary phthisis. She came direct from Silesia, where she had been a hospital sister in a Breslau hospital. On November 5—*i.e.*, seventeen days after her arrival in the sanatorium—she complained of insomnia and headaches. Some tenderness was elicited over the upper cervical vertebræ, and movements of the head were painful. As the patient had come from a meningitis-ridden area in Silesia, cerebrospinal meningitis was suspected. She was accordingly isolated, and treated with meningococcal serum. Meningococci were isolated from her naso-pharynx on two occasions in the first week of the disease. Forty-five persons in the sanatorium, including patients with whom she had sat at meals, physicians, sisters, and servants, etc., were examined, but no carriers were found. The conclusion was reached that the woman must have been already a carrier when she left Breslau on October 16. No other cases occurred in the sanatorium, and Bochalli suggests this was probably due to the fact that the patient during the early part of her stay in the sanatorium had had practically no opportunity of spreading infection.

On the other hand, although auto-infections may undoubtedly occur, it cannot be denied that the great majority of these carriers never develop symptoms pointing to meningeal infection, and in this respect they are in marked contrast to children in whom the susceptibility to meningeal infection is notorious. Flatten put forward the view that the susceptibility of children was only apparent, and attributed it to the fact that the child had greater opportunities of being infected. He asserted that in the meningitis-ridden industrial areas young children were in great excess ; but, as Busse has pointed out, if one takes Flatten's own figures, one finds that the number of children under six years at Königshütte was 20·8 per cent. of the population ; but, in spite of this, they formed no fewer than 57·3 per cent. of the cases—viz., 559 out of 975—so that the number of cases in this group was out of all proportion to the size of the group.

Another hypothesis has been put forward by Jehle—viz., that the large proportion of carriers found in mining districts was to be explained by the favouring influence of the moisture in the mines on the growth and vitality of the meningococcus. For this hypothesis there is no sufficient ground, as the extra-corporeal life-history of this organism is, under all circumstances, short, and a more intelligible explanation for the greater frequency in such conditions would certainly be found in the greater crowding in the mines leading to the wider spread of the coccus from throat to throat.

A similar wide spread has been shown to take place in other crowded populations—*e.g.*, in army barracks.

It is impossible at present to give a satisfactory explanation of the greater liability of older persons to become carriers without showing meningeal symptoms, and the greater liability of younger persons to be attacked by meningeal invasions. The explanation must be left for further research.

Various observers have suggested that trauma (head injuries) and alcoholic excess may predispose to meningeal infection in a carrier, and it is not at all unlikely that in adult carriers such factors may determine a blood invasion, with consequent meningitis. The view is becoming more and more widely held that the meningococcus reaches the meninges by way of the blood-stream. Frequent recoveries of the meningococcus from the circulating blood have been reported in the early days of the disease, and it would appear, indeed, that the meningococcus may not always exert its destructive action solely on the meninges. Herford has observed a case of meningococcal septicæmia without symptoms of meningitis; and Jacobitz (1907) has reported a small series of meningococcal pneumonias without meningitis in the course of a garrison outbreak.

On the Factors concerned in the Rise and Fall of a Cerebrospinal Epidemic.

It will be abundantly evident from the data adduced in previous pages that the number of "healthy" carriers in an epidemic of cerebrospinal meningitis may largely exceed the number of actual cases. The carriers may, in fact, during the height of an epidemic, be ten, or even twenty, times more numerous than the cases, although it is quite possible, as some observers have suggested, that, provided the examination of the healthy entourage of a patient is made at the shortest possible interval after notification, the actual number of carriers found may be small. If, indeed, bacteriological aid could be requisitioned early enough, and suitable hygienic precautions taken, there is little doubt that the number of cases amongst the more susceptible members of the population would be considerably curtailed, as not only the infectivity of each carrier, but the total number of carriers, would be diminished. The part played by the healthy carriers in the spread of an epidemic, once it has arisen, does not require to be insisted upon. By comparison, the influence exerted on the spread of the disease by the actual case of meningitis is probably quite inconsiderable. The problem of the rise and fall of the epidemic is, however, far more difficult. In typhoid-fever outbreaks the evidence incriminating the chronic typhoid carrier as the starting-point of an epidemic is overwhelming; but in cerebrospinal outbreaks it has rarely been possible to point to a particular meningococcal carrier or carriers as the initial sources of infection. Though, however, such evidence is difficult to produce, largely by reason of the rapid multiplication of carriers, there can be little doubt, from the data we have adduced relating to the occurrence of chronic meningococcal carriers, that these persons form the bridge between one epidemic and the next. In outbreaks of cerebrospinal meningitis, however, the seasonal factor cannot be neglected, and it may be that meteorological conditions (influence of cold, throat catarrhs, etc.) determine, in the first instance, a multiplication of carriers in the neighbourhood of chronic carrier foci. Assuming the presence of a susceptible population round these carrier groups, one can readily conceive how an epidemic may be started. Bruns and Hohn, as already mentioned, found that the number of contact carriers in proportion to cases fell during the decline of the epidemic. Such an observation would be of great interest if confirmed, but at present it is idle to speculate whether to assume a gradual loss of virulence of the meningococcus as the epidemic declines, or an increased power of throwing off the germs on the part of those on whose throats they alight, owing to the altered climatic conditions in the summer months and the consequent diminished susceptibility to catarrhs.

It is somewhat curious that little or no evidence is forthcoming in regard to the occurrence of carriers in the neighbourhood of sporadic cases of meningococcal meningitis (so-called "post-basic meningitis"). Such cases are continually cropping up, but they do not appear to give rise to any epidemic prevalence. That such cases may give rise to carriers, however, is suggested by the fact that attacks have been known to occur in members of the same family at considerable intervals. No essential differences have been found between the meningococci associated with post-basic cases and those met with in times of epidemic (Wollstein, 1909; Arkwright, 1909, etc.). Great care, however, must be taken in the diagnosis of these sporadic cases in view of the fact that a certain proportion of cases clinically indistinguishable from meningococcal post-basic meningitis, have been found to be due to other organisms. Thus McDonald (1908), Batten (1910), Ritchie (1910), and others in this country, have recovered *Bacillus influenzae*, or hæmophilic influenza-like organisms in certain cases of meningitis in children simulating clinically meningococcal post-basic meningitis.

ON THE PRESENCE OF SPECIFIC ANTIBODIES IN THE BLOOD OF CONVALESCENTS AND HEALTHY CARRIERS.

Under the above heading very little evidence can be adduced, either of a positive or negative character, as the subject does not appear to have been investigated to an extent at all commensurate with its importance from the pathogenetic point of view. The agglutinin content of the blood serum of convalescent cases has, indeed, received some scant attention, and, as might be expected, not a few cases have been recorded in which the specific agglutinins have persisted in the blood serum for a long period after recovery. Thus Bettencourt and França (*loc. cit.*) were able to demonstrate a marked agglutinating power of the blood twelve to fourteen months after the commencement of the infection. In one convalescent the serum had a titre 1 in 1,000. Such a high titre must be considered exceptional in the light of results obtained by other observers. Variations in the agglutinability of meningococcus strains have, in fact, proved a source of great difficulty in serological studies, and it is impossible for that reason to draw valid comparisons between sera titrated with different strains. Von Lingelsheim, who examined a large series of cases, found that, after the twenty-first day of the disease, the number of sera which gave definite agglutination fell markedly (from 52·7 per cent. to 26·7 per cent.), and the titres he obtained, both during the course of the disease and later, were always low ; in one case only reaching 1 in 200, and in two cases only reaching 1 in 100.

Macgregor (1910) performed agglutination experiments with the sera of a number of cerebrospinal cases, and found that the agglutinin content bore some relation to the initial features of the infection, and particularly to the duration of the initial toxæmia. Thus, in very acute infections with severe toxæmic symptoms, and ending fatally, no agglutinins developed. Nor was there any appreciable development in cases which were of a chronic character from the outset. Agglutinins (titres, 1 in 80 to 1 in 100) were developed only in certain cases with acute onset and symptoms of severe general infection, which suddenly abated in the manner of a crisis early in the disease.

Cohn (1909) had an opportunity of testing the agglutinin content of the serum of three adult individuals who, at intervals of two years three months, two years two months, and one year three months respectively, after an attack of cerebrospinal meningitis, returned to hospital suffering from various sense disturbances and paresis (hydrocephalus). The serum of one of the cases still agglutinated the meningococcus in a dilution of 1 in 100. That of another gave an agglutination in a dilution of 1 in 1,000 ; while the third (examined, however, post mortem) was negative. Control human sera did not agglutinate the meningococcus in a higher dilution than 1 in 20.

Bactericidal substances have been demonstrated by McKenzie and Martin (1908) in the sera of recently-recovered cases, but not in the cerebrospinal fluid. On this fact they based a method of treating acute cases by inoculating them intraspinally with serum from convalescents.

Opsonic substances have also been demonstrated by Houston and Rankin (1907) in the sera of convalescents. Eight such were tested at periods varying from one to forty-seven days after recovery, and in five of them very high indices were obtained. Three of these five positive cases also gave marked agglutination.

In the series examined by Macgregor (*loc. cit.*), specific opsonin was found in the blood many weeks after recovery in some cases. In others, the opsonic power seemed to disappear comparatively rapidly. Examinations up to thirteen weeks were made in some cases after recovery.

HEALTHY CARRIERS.

We have in a previous section pointed out the difficulty of deciding whether a pharyngitis in an otherwise healthy carrier is a consequence of meningococcal infection, and have come to the conclusion that the balance of probabilities is in favour of this supposition. Naturally, the demonstration of specific antibodies in the sera of such cases would add material support to that view. Evidence of this nature would be still more valuable in the case of the healthy carrier who presents little or no symptoms of naso-pharyngeal catarrh. Unfortunately, we cannot yet bring forward evidence that can be considered decisive.

Ostermann (1906) tested the blood of carriers at different periods for agglutinative powers towards the meningococcus, but in no instance was a positive result obtained.

Jacobitz (1907) obtained an agglutinative titre of 1 in 500 in the serum of a case of meningococcal pneumonia, without symptoms of meningitis. The illness commenced with a severe tonsillitis, and pneumonia later supervened. From the rusty sputum the meningococcus was recovered in pure culture.

Cathoire (1910), starting out from the hypothesis that the comparative immunity of healthy carriers is due to development of antisubstances in the serum following the meningococcal invasion of the naso-pharynx, proceeded to test the sera of ten healthy carriers for their opsonin and agglutinin content. These persons had harboured the specific cocci in their throats for several months, medication having proved of no value in dislodging the germs. Agglutination in all cases was negative, even in a dilution of 1 in 20 ; but by employment of the ordinary opsonic technique, very high indices were found—varying, in fact, from 1·6 to 8·1 (average of 10 cases, 4·01). These high values are certainly striking, and they suggest a close similarity with those found by Houston and Rankin in the later period of the disease and in convalescence. The question undoubtedly requires reinvestigation, as opportunity offers. Should it be proved beyond cavil that the serum of healthy carriers contains specific antisubstances to the meningococcus, much of the argument in support of the view that in these cases the meningococcus is present as a mere saprophyte would fall to the ground. Not only so, but a reasonable explanation might be afforded for the great difference of susceptibility to meningeal infection exhibited by young children and adult healthy carriers respectively.

TREATMENT OF MENINGOCOCCAL CARRIERS AND PREVENTIVE MEASURES.

Medicinal treatment directed towards the removal of the specific micro-organisms from the throats of carriers, and thereby rendering the latter innocuous to their surroundings, has been applied in a variety of ways without appreciably diminishing the period of their physiological sojourn in the throat. The drugs and local applications which have been employed by various writers, such as antiseptic gargles, silver salts and organic silver preparations, potassium permanganate, zinc sulphate, medicated sprays, orthoform, turpentine inhalations, etc., have in most cases failed to eradicate the disease germs entirely, from their nidus in the throat. The employment of pyocyanase in the form of spray has been recommended by Jehle (1907), and later strongly advocated by Huber (1908), who asserts that those carriers who have no obvious throat symptoms, and in whose throats the cocci have not gained any definite footing, can readily be cured by two or three sprayings with pyocyanase, while those who show symptoms indicating that the cocci are definitely established in the mucosa are entirely uninfluenced by this drug. Now, while admitting that this distinction is a valid one, it by no means follows that the pyocyanase has been the essential cause of the disappearance of the cocci in the former type of carrier, as it has frequently been noted that in such carriers, in the absence of treatment, the sojourn of the cocci in the throat may not extend over a few days (Herford). In the latter type of carrier it may be stated as probable, in the absence of more precise knowledge on the subject, that the sojourn of the cocci in the throat lasts probably as long as, or longer than, in the case of actual convalescents. In the chapter on Typhoid Carriers we have referred to Scheller's type of carrier ("Zwischenträger"), in which the organisms lead a short and purely saprophytic existence. Though, perhaps, the evidence for postulating such a form is not very satisfactory in the case of typhoid, the term might reasonably be applied to the first type of meningococcal carrier mentioned by Huber, in the absence of further knowledge with regard to serological changes in the host as the result of the temporary presence of meningococci in the throat.

Vincent and Bellot (1910) have recently advocated, as the result of their experience in the French Army, the following inhalation:

℞	Iod.	ʒv.
	Guiacolis	ʒss.
	Acid. thymic.	gr. iv.
	Sp. vin. rect.	ad ℥viii.

A small amount of this is placed in a porcelain capsule and heated, and the vapour inhaled. The same authors also apply wool tampons impregnated with iodated glycerine to the mucous membrane.

℞	Iod.	gr. vii. ss.
	Pot. iod.	gr. xv.
	Glycer.	℥i.

By such methods they claim that the cocci may be made to disappear in four days.

It is, however, the unanimous opinion of most writers of experience that the local drug treatment is of little avail in diminishing the period of potential infectivity of these carriers; but, none the less, the use of these remedies should not be dispensed with, if by their means a reduction in the number of the cocci in the throat can be attained, thus rendering the potential infectivity of the carrier at any given time much less than otherwise. Especially is such treatment of value if the carrier is compelled to cough frequently, or has the habit of frequent expectoration. We have seen that in the typhoid carrier the bacillary depots are mainly, if not exclusively, located in the mucosal papillæ of the gall-bladder and bile-tracts, and that surgical treatment in chronic cases would afford a prospect of radical cure if it could be made sufficiently extensive. In the meningococcus carrier, on the other hand, we have no such definite evidence of the histology of the pharyngeal condition; but it would appear likely that similar deeply-seated meningococcal depots are also present, which can only to a very slight degree be influenced by medicinal treatment, and which must abide Nature's time of cure. Naturally, other methods, such as the local application of antimeningococcal serum or the inoculation with meningococcal vaccines, may be found to assist Nature materially in her work of cure; but so far we have no evidence to adduce on this point.

Von Lingelsheim has discussed the question of dividing carriers into dangerous and less dangerous types, according as the catarrhal symptoms are more or less severe. There can be no question that the co-existence of pharyngeal catarrh necessitating frequent coughing, must increase the dangerousness of the carrier, and it is fortunate that there are these qualifying considerations, as they considerably compensate for the cumbrous and possibly impracticable method of isolation of carriers. There is no evidence for or against the view that the cocci in the carriers' throats are of diminished virulence. Several writers, impressed with the fact that none—or at least very few—of their healthy meningococcal carriers either developed the meningitic form of the disease themselves or gave rise to it in others, have assumed that the specific cocci in the throat undergo involution changes of a degenerative character during their saprophytic existence, and coincidently, in all probability, lose much of their capacity to produce further infection. In the absence of further evidence, such statements can neither be supported nor challenged at the present time; but it is hoped that experimental research on the carrier state may throw light on this matter.

Finally, there is the question of isolation to be discussed, and there can be no doubt that, if this measure can be effectively carried out, and for a sufficient length of time, a marked reduction in the number of cases would be expected. The obvious difficulties involved in such a measure are—(1) the number of the carriers which may exceed (as already mentioned) the number of cases ten times, and (2) the expense.

Now, it has been pointed out by Flatten that, provided the search for carriers is carried out immediately a case of infection is notified in a family, the number of carriers found may be very small. Trautmann also came to similar conclusions from his work in Hamburg. The rapidity with which one carrier infects a community so that large carrier groups are formed, can only be combated by prompt examination of all the members of the family and entourage of the meningitis patient. In order to secure this prompt examination of the entourage, it would be necessary, as Flatten and others have suggested, to institute a system of travelling laboratories, which could be readily transferred to the epidemic area. Isolation could then be undertaken, and probably would be submitted to in working-class districts, provided wages and all expenses were paid during the period of isolation. It is not likely, however, that this measure will commend itself to public health authorities—at any rate, in this country, where epidemics of the disease have been very infrequent.

In both the French and German Armies the isolation of meningococcal carriers has been practised in times of epidemic.

That the isolation is not very readily tolerated in some cases may be gathered from the following observation of Sacquépée and Bellot. They mention the fact that a soldier who was retained for a considerable period under isolation as a meningococcal carrier became exceedingly morose and melancholic, and threatened to do away with himself.

Apart from compulsory notification, which should be enforced not only during epidemics, but in epidemic-free intervals, public health authorities should concentrate their energies on the problem of controlling the movements of carriers, the issue of suitable instructions warning carriers of the risks they incur, not only of infecting the more susceptible members of the community, but also, possibly, themselves (from trauma, alcoholic excess, etc.). Steps should be taken immediately on the outbreak of an epidemic to discover by bacteriological methods the healthy carriers in the entourage of notified cases, and medicinal treatment should be employed to render the potential infectivity of such carriers as small as possible. Also, special instructions should be given to carriers who suffer from catarrhal conditions of the throat, necessitating frequent coughing and expectoration. With regard to schools, many observers are of opinion that these do not constitute very important breeding-places of the meningococcus in times of epidemic, probably because of the fact that children are not so much addicted to coughing and expectoration.

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CHAPTER VI

DYSENTERY

I. BACILLARY DYSENTERY.

Owing to the confusion between amœbic and bacillary dysentery which formerly prevailed, and still persists to some extent, on account of their clinical similarity, reliable observations as to the epidemic prevalence, method of transmission, and sources of infection of either disease have been difficult to obtain, especially in tropical countries. However, a sufficient number of epidemics of bacillary dysentery have now been carefully investigated to enable some of the chief points relating to the spread of the disease to be stated with a considerable degree of assurance.

Since Shiga (1898) and Kruse (1900) described the bacillus of dysentery, as found by them in epidemics in Japan and Westphalia, much work has been done, and the bacillus has been found in cases of dysentery in all quarters of the globe. In the same year in which Kruse's researches were published, Flexner (1900) described the bacillus now usually known by his name, which he had isolated from cases of dysentery at Manila in the Philippines.

The divergent characters shown by these different races of *Bacillus dysenteriae* have been a fruitful source of controversy and confusion; but it is now well established that the strains discovered by Shiga and Kruse are identical in all respects, and that members of the same race have been found in many parts of the world, without any essential variations in their chief characteristics. The *B. dysenteriae* described by Flexner, on the other hand, though possessing an equal claim to be a cause of dysentery, must be considered merely as the representative of a group of closely-allied bacilli, which differ slightly among themselves as regards cultural, serological, and biological characters, but still have features in common, which separate them with yet greater distinctness from the Shiga-Kruse group.

The distinctive characters of the two groups are fairly definite, and include both cultural and serological differences.

Kruse (1907) was impressed by the distinctive characters of the Flexner strains, and believed that the clinical disease with which they were associated was always of a mild type. He therefore felt justified in applying to such strains the term *B. pseudodysenteriae.* This name is now very generally abandoned, since this group has been found to be associated with some very severe epidemics of dysentery.

Severe cases of dysentery due to the group of which Flexner's bacillus is a member have been described by Ruffer and Willmore (1910) as occurring at El Tor in Arabia. It is probably true, however, that the sporadic and milder cases of dysentery have most frequently been found to be associated with the Flexner group.

The evidence pointing to the conclusion that the *B. dysenteriae* is the exciting cause of dysentery will be dealt with more fully later. The chief arguments supporting this contention are the following:

1. The detection of the bacillus in large numbers in the excreta in almost all cases of the disease.
2. Its great rarity in healthy persons or those suffering from other diseases.
3. The pathogenicity of some forms of *B. dysenteriae* for laboratory animals.
4. The agglutination of the bacillus by the serum of patients.
5. The curative effect on human cases of the serum of horses immunized with pure cultures of the bacillus.

An outbreak of the disease has seldom been conclusively traced to a person who has carried over the *B. dysenteriae* from a former epidemic. This deficiency in the direct evidence has given rise to some doubt as to the efficacy of "carriers" in this disease. There is, however, no doubt that convalescents after severe and also after very mild attacks of dysentery continue to pass the bacillus in the stools in large numbers for a considerable time after the symptoms have ceased. Moreover, in some cases slight relapses occur, which cause a prolonged, though often intermittent, excretion of the *B. dysenteriae.*

These cases form a large reservoir and numerous active distributing centres for the bacilli. The infecting *B. dysenteriae* reaches fresh patients directly by use of the same closets, which are especially apt to be fouled by persons suffering from griping pains and tenesmus, or less directly by such means as food infected by the hands, dust, or flies, or, in some cases, perhaps through water.

Which of these routes is the commonest in a given epidemic depends on the special circumstances. In any case, carriers are often at least as effective polluters of the closets, soil, food, etc., as the acute cases of dysentery, and are very important sources of infection. The carriers are, however, not often completely free from all history of illness, as so frequently happens in the case of diphtheria carriers, and they usually have recently recovered from an attack of dysentery, unlike the chronic typhoid carriers, who may continue to be hosts of the bacillus for years.

The greater efficacy in some respects of the carrier as compared with the sick person, depends partly on his greater mobility and the longer period during which he is infective, and partly on the want of care exercised by those around him, which is due to the fact that he is an unsuspected source of danger.

Epidemics of dysentery associated with one or other of the races of *B. dysenteriae* have been investigated in the tropics as well as in various parts of the temperate zones, including several of the countries of Europe.

In asylum dysentery the *B. dysenteriae* has been repeatedly found in several countries. Occasionally the *B. dysenteriae* of the Shiga-Kruse type has occurred in the dysentery of the insane, but more often the strain isolated belongs to the Flexner, or mannite-fermenting, group.

II. BACTERIOLOGY.

The various strains of *B. dysenteriae* form a very closely-allied group of Gram-negative bacilli, which agree with the other known pathogenic intestinal bacteria in not fermenting lactose. The *B. typhosus* appears in its cultural characters to approach most closely to *B. dysenteriae*, as neither the causal organism of typhoid fever nor that of dysentery forms gas from the sugars which it ferments. The *B. dysenteriae* is, however, non-motile, and in this important characteristic differs from *B. typhosus* and *B. paratyphosus*.

Two main groups of *B. dysenteriae* are recognized, either of which may be associated with severe epidemic dysentery. The first of these groups consists of a very uniform series of strains. To this belongs the bacillus originally described by Shiga (1898) in epidemic dysentery in Japan, and that described by Kruse (1900) as the cause of an epidemic in Westphalia. It has since been found in cases of dysentery in many countries. The *B. dysenteriae* (Shiga-Kruse) forms acid from glucose only amongst the carbohydrates. No indole is formed in the broth cultures. It is remarkable for the high pathogenicity of the cultures, which produce death with characteristic lesions in rabbits, when injected intravenously in as small a dose as one-twentieth to one-fiftieth of a loop of an agar culture. In broth cultures a toxin is formed which can be obtained free from bacilli by filtration. For a rabbit of 1,800 grammes the lethal dose of toxin may be 5 c.c. subcutaneously, or 0·08 to 0·2 c.c. intravenously. Toxin of this high degree of concentration is best obtained by growing the bacillus for fifteen to twenty-one days in special alkaline broth, according to Doerr (1908). The degree of toxin production varies, however, with the particular strain used, the batch of broth, etc.; but the strains of this group always form toxin. An agglutinating serum prepared with a Shiga-Kruse strain will agglutinate any other member of this group in a dilution approximating to that of the homologous strain. Sera which agglutinate in a dilution of 1 in 10,000 can be obtained.

Members of the other group, of which the representative strain is that described by Flexner in 1900, have the property of producing acid from mannite as well as from glucose, and most of the strains, including Flexner's original bacillus, form indole in broth cultures. No appreciable amount of toxin is formed in the cultures, and the bacilli are much less pathogenic for laboratory animals. Rabbits generally survive a dose of half a loop of an agar culture intravenously.

Sera produced by immunizing rabbits with strains of this group will not agglutinate Shiga-Kruse strains, even when agglutinating the homologous strain in a dilution of 1 in 5,000.

It sometimes happens that a Shiga-Kruse agglutinating serum, when slightly diluted—*e.g.*, 1 in 100—will clump strains of the mannite-fermenting group.

The mannite-fermenting group of *B. dysenteriae* is made up of far less uniform strains than the Shiga-Kruse group, and very numerous subgroups have been described as occurring in different epidemics and places. These different strains are best distinguished by the fermentation of carbohydrates. Castellani's method of absorption of agglutinins, which was used for differentiating this group by Kruse (1907), has since been found unsatisfactory by Lentz (1909), Morgan (1911), and Bainbridge and Dudfield (1911), for this group.

One subgroup—viz., that described by Strong (1900)—stands alone, in that acid is formed by it from cane-sugar, and the agglutinating serum made with it, does not react with any other strains, nor do their sera agglutinate Strong's bacillus in high dilution. This strain has probably only been isolated on one occasion. The other subgroups—*e.g.*, those described by Flexner (1900) in the Philippines, by Hiss and Russell (Hiss, 1904) in America, by Aveline, Boycott and Macdonald (1908), Macalister (1910), and Morgan (1911) in England, by several workers in Germany, and by Ruffer and Willmore in Arabia—show variations in the fermentation of additional carbohydrates (maltose, dextrin, sorbite), in the production of indole or in agglutination. They are usually agglutinated by fairly high dilutions of agglutinating sera, prepared from one or other of the well-known members of this group—*e.g.*, *B. dysenteriae*, " Y " of Hiss and Russell.

These strains can be distinguished amongst themselves to some extent by their agglutination with sera prepared from certain of the strains of the mannite-fermenting group. The absorption of agglutinins does not appear to be a satisfactory method of classification, since the differentiation arrived at by this procedure is too fine, and would make a new subgroup of the strains from almost every outbreak, besides giving inconsistent results (Bainbridge and Dudfield, 1911 ; Morgan, 1911).

M. Wassermann (1912) has more recently related similar difficulties which he has encountered in an attempt to classify mannite-fermenting strains by the absorption method.

The whole of this group was named by Kruse *B. pseudodysenteriae*, on account of the want of conformity of the strains with the Shiga-Kruse variety of *B. dysenteriae* and their inability to form toxin. He maintained that these strains were associated with a mild type of the disease which occurred chiefly in an endemic rather than epidemic form.

These contentions of Kruse have to some extent been confirmed by subsequent observers, and bacilli of the mannite-fermenting group have more often been found in sporadic cases than the Shiga-Kruse bacilli, and have sometimes been detected in persons who are healthy or suffering from other complaints, and not in contact with cases of dysentery. For example, the majority of the strains isolated by Ledingham in the course of an investigation of typhoid convalescents and suspected typhoid carriers, were not associated, so far as could be ascertained, with cases of bacillary dysentery, clinically recognized as such.

These last-mentioned strains were thoroughly examined by Morgan (1911).

It is, moreover, the mannite-fermenting type of the *B. dysenteriae* which is commonly found in endemic asylum dysentery. Nevertheless, the bacilli of this group were also found in severe epidemic dysentery in Arabia by Ruffer and Willmore (1909), and Kruse (1907) himself described a very severe and acute "uræmic" case due to a mannite-fermenting bacillus.

The great number of variations in the group called *B. pseudodysenteriae* by Kruse has raised the question whether these strains are really distinct or are continually changing without any fixity of character. The strains of bacilli occurring unexpectedly in small numbers and quite sporadically in typhoid carriers, etc., suggest the doubt whether all similar bacilli should be regarded as true *B. dysenteriae*, even when they differ from the main types in slight peculiarities of sugar fermentation, such as the production of acid from sorbite (Morgan, 1911 ; Tebbutt, 1912). It seems, on the whole, best that they should be considered *B. dysenteriae*, as there is no more reason to exclude them from the group than there would be to exclude the somewhat aberrant strains isolated by Ruffer and Willmore in epidemic cases of dysentery at El Tor. The acute outbreak of dysentery recorded by Bainbridge and Dudfield (1911) was also associated with a sorbite-fermenting *B. dysenteriae.*

In opposition to the view that variation is constantly going on, Kruse (1907) brought forward the following considerations :

1. The strains remain constant in culture.

2. The same person is found to yield only one strain at different stages of his illness.

3. The strains from the same epidemic all belong to the same subgroup.

For most epidemics these propositions appear to be approximately true, though slight variations in sugar fermentations have occurred in the course of prolonged artificial culture, and strains of *B. dysenteriae* occur, as is the case with *B. typhosus*, which are inagglutinable when first isolated. It does occasionally happen that strains belonging to different subgroups have been isolated from the same person at different times, as in the case narrated by Loesener (1910). Not infrequently also Ruffer and Willmore (1909) found cases due to mixed infection with different subgroups.

It is not unlikely that the *B. dysenteriae* (mannite-fermenting type) is subject to occasional changes in its characteristics, and is much less a fixed species than some other pathogenic organisms —*e.g.*, *B. typhosus*. The subject of mutations or variations of this group has at present merely been touched upon by workers.

The term " pseudodysentery " is not now generally used, but the marked distinction between the two groups of bacteria is constantly emphasized by workers in fresh fields.

The cultural methods employed for discovering, isolating, and identifying the *B. dysenteriae* present in dejecta are very similar to those found useful in examining typhoid patients and for isolating the *B. typhosus* from carriers. The stools are first carefully examined for mucus, since flakes of muco-pus, or streaks of mucus, are the most favourable parts in which to find the *B. dysenteriae*. No difficulty occurs when small stools consisting only of blood and mucus are passed, but when the motions are larger and fæcal, it is not always easy to hit upon the most favourable portion. In the case of a solid stool, the surface is sometimes covered in part with mucus which contains the bacilli. Liquid stools are best examined for blood and mucus by placing a small portion in a sterile Petri dish.

A platinum loopful of the part selected is then plated on the surface of lactose-agar plates by rubbing the material well over the surface of the first plate with a bent glass rod, and then inoculating a second and third plate with the same rod, without adding fresh material. Several selective media may be used for this purpose, each containing an inhibitant for some of the micro-organisms present, and an indicator, such as litmus or neutral red, to enable those colonies which do not form acid from lactose to be readily picked out.

MacConkey's bile-salt-neutral-red-lactose-agar plates are perhaps the best for the purpose ; but the Conradi-Drigalski medium containing crystal-violet and litmus and many other media, have been much used abroad.

On MacConkey's medium the colonies of *B. dysenteriae* appear on the first day as colourless colonies in the less crowded parts of the plates. In acute cases of the disease, especially when there is an infection with bacilli of the Shiga-Kruse type, the colonies of *B. dysenteriae* are often very numerous, and other organisms may be few. At later stages of the disease only very few such colourless colonies may be found.

The suspected colonies are picked off, inoculated into broth, and incubated at 37° C. The culture must be examined in a hanging drop for the motility of the bacilli after six hours' growth, and when a good culture in the broth has been procured, glucose and mannite litmus-peptone-water tubes are inoculated. The broth culture is incubated for five days, in order that it may be tested for indole by the paradimethylamidobenzaldehyde test. The tubes containing carbohydrate media should be provided with Durham's tubes for the observation of gas production.

	Glucose.	Mannite.	Maltose	Cane-Sugar.	Sorbite.	Indole.	Dextrin.
Shiga-Kruse	a	—	—	—	—	—	—
Flexner	a	a	a	—	—	+	a
" Y " Hiss and Russell	a	a	a	—	—	+	a
Duval	a	a	a	—	—	+	a
Kruse, D.	a	a	—	—	—	+	a
Strong	a	a	a	a	a	+	—
Willmore, Tor (22) ..	a	a	a	—	—	+	—
Willmore, Tor (167) ..	a	a	—	—	a	+	—
Willmore, Tor (12, 10) ..	a	a	—	—	—	—	a

a = acid. + = indole formed.

The above table shows the more important variations in the carbohydrate reactions as exemplified by certain recorded strains.

A more complete examination of the culture isolated is made by inoculating peptone-water tubes containing cane-sugar, dulcite, and sorbite, and also litmus milk An agar slope should also be inoculated and incubated at 37° C., in order to provide growth with which to test the agglutinating reaction of the strain.

For the identification of the *B. dysenteriae*, agglutinating sera of high value for at least two strains (Shiga-Kruse and the " Y " strain of Hiss and Russell) must be used, or if only the presence or absence of *B. dysenteriae* is sought for as a preliminary examination, without further inquiry into the exact strain, a polyvalent agglutinating serum prepared with several strains is most useful.

It is important that the agglutinating serum should have a high titre (at least 1 in 1,000), and that a control with normal serum should be set up, in case spontaneous agglutination of the emulsion occurs.

The colonies from the plates may be emulsified and used directly for microscopic agglutination if it is important to arrive at a diagnosis in the least possible time.

Morgan (1911) found that all the mannite-fermenting strains were agglutinated by serum prepared with Hiss and Russell's " Y " strain in sufficient dilution to justify a diagnosis of *B. dysenteriae.* A finer differentiation of the various mannite-fermenting strains may be attempted by Castellani's method of absorbing the agglutinins from an immune serum. This method, however, as stated above, is not of much value for this purpose.

The detailed identification of the exact subgroup to which a *B. dysenteriae* belongs may be of importance when the source of the infection is under consideration, and it is desirable to know whether two persons are infected with the same strain. It may also be of importance when therapeutic antitoxic sera are to be employed, but these sera are generally polyvalent.

The serum of patients and persons suspected of carrying the dysentery bacillus should be examined as to its power of agglutinating the strain of *B dysenteriae* whose presence is considered likely. Agglutinins do not as a rule appear till after the first few days or the first week of illness, and have frequently disappeared again in a fortnight, according to Mayer (1910) ; but they may last six months or longer after the cessation of symptoms.

If the infection is with one of the mannite-fermenting group, the patient's serum agglutinates only strains of that group, and often only those of the same subgroup. The reaction should not be considered positive unless it occurs in a dilution of 1 in 100, but it may be obtained even when 1 in 500 dilution is used (Mayer, 1910). When a Shiga-Kruse strain is the causal organism, a positive reaction of 1 in 50 with a bacillus of this group is sufficient for diagnostic purposes. The serum from such a patient will often agglutinate a mannite-fermenting strain in a dilution of 1 in 50, but this may occasionally occur with normal serum, and is of no significance.

GEOGRAPHICAL DISTRIBUTION OF BACILLARY DYSENTERY.

The two main groups of bacillary dysentery are not limited at the present day to different countries in their geographical distribution, though certain localities are no doubt specially liable to outbreaks of one or other variety. This widespread distribution very probably took place at a period antecedent to the recognition of the *B. dysenteriae*, and need not be taken as evidence of mutation going on in recent years.

Wars and the movements cf armies have played a large share in the distribution of these bacilli. This was especially remarked in Germany after the war of 1870-71. When the soldiers who had been attacked by the disease during the war returned to their homes some of them were still acting as carriers of the *B. dysenteriae*, and set up epidemics in several parts of Germany.

The *B. dysenteriae* of Shiga and Kruse has been reported as causing epidemics in Germany, especially in East Prussia ; in one asylum in England (Eyre, 1904) ; in Scotland ; Italy ; France ; Russia ; Tunis ; South-West Africa ; Uganda ; Arabia (Ruffer and Willmore, 1909) ; India ; Ceylon ; Japan ; the Philippines ; the United States ; and in numerous other centres.

Dysentery attributed to the mannite-fermenting type of *B. dysenteriae* has been prevalent in the Philippines, China, Japan, West Asia, and also in Austria, Germany, France, and North America. For example, the *B. dysenteriae* "Y" of Hiss and Russell, which is one of this subgroup, has been described as occurring in Germany by Kruse, Lentz, Liefmann and Nieter, etc. ; in North America in the summer diarrhœa of children by Duval ; and by Shiga in Japan and in Sumatra.

In England, dysentery is practically confined to asylums for the insane, except for a very few sporadic cases of ulcerative colitis (Hawkins, 1909), and cases of infantile diarrhœa in some epidemics. Morgan (1907), though he failed to find dysentery bacilli which conformed strictly either to the Shiga-Kruse or to the Flexner type, nevertheless found some strains which were perhaps variants of the mannite-fermenting group in summer diarrhœa in London. Strains of the mannite-fermenting group have been found in all but one of the asylum epidemics investigated in England or Germany. Recently in London, Bainbridge and Dudfield (1911) have recorded a small epidemic of bacillary dysentery in children associated with a member of the mannite-fermenting group.

EVIDENCE OF THE CAUSAL CONNECTION OF B. DYSENTERIÆ WITH DYSENTERY.

The claim which the several varieties of *B. dysenteriae* have to the title of "causal micro-organisms of dysentery" is based on—

1. The frequency with which a particular variety of the bacillus is found in cases of the disease in a given epidemic and the comparative rarity with which it is found in persons under similar circumstances who are not associated with cases of dysentery.

Aveline, Boycott, and Macdonald (1908) found *B. dysenteriae* (Flexner) in 17 out of 19 acute cases of asylum dysentery, whereas of 26 controls, many of which were from the same wards, none yielded the bacillus.

Mayer (1910) found that 51 out of 53 cases of illness in an infantry regiment yielded the same variety of *B. dysenteriae* (mannite-fermenting group), whilst from only 22 apparently healthy men out of 573 in the same regiment could *B. dysenteriae* be isolated. Twenty-eight of the men had severe attacks of dysentery, and 27 of these yielded the bacillus at the first examination. The remaining 23 patients were clinically cases of catarrhal diarrhœa, and 22 of these were found to be infected by the bacillus. One further patient out of the total 53 was shown to be probably infected, by the fact that his serum agglutinated the bacillus found in the other cases. Only 1 case occurred in which the diagnosis could not be verified either by isolation of the bacillus or an agglutination test.

Similar evidence is forthcoming from other epidemics, but it has not been found possible to demonstrate the presence of the bacillus in so large a proportion in all outbreaks.

Fischer (1910), during an epidemic in Essen, obtained evidence of infection by *B. dysenteriae* in 64 out of 96 clinical cases. The bacillus was not isolated in all the 64 patients, but in the case of those patients from whom cultures could not be obtained, their serum gave a positive agglutination reaction.

Of the 64 positive results, 58 were apparently due to the Shiga-Kruse race of *B. dysenteriae,* and 6 cases to the Flexner, or the "Y," type. These 6 cases were not shown to be connected with the remainder of the outbreak, and 5 of their number ran quite a mild course.

2. The serum of patients usually agglutinates the bacillus with which they are invaded. The reaction does not as a rule occur till after the first few days of the illness, as in the case of

other infectious diseases. This is strong evidence that the illness from which the patients were suffering was due to a true infection with the *B. dysenteriae*, which has caused a reaction on the part of the patient, and a resulting appearance of agglutinins in the blood (Kruse, 1900 ; Mayer, 1910 ; Lüdke, 1911).

3. Further evidence that the *B. dysenteriae* is capable of producing pathological lesions is shown by the highly toxic nature of the cultures of the Shiga-Kruse bacillus. A tenth or less of a loopful of a living agar culture, or one-fifth of a c.c. of a filtrate of a broth culture given intravenously to a rabbit, will produce death, with intense inflammation of the large intestine (Todd, 1903 ; Doerr, 1908). The bacilli of the mannite-fermenting group are much less toxic.

4. An immune serum obtained from a horse by inoculation of pure Shiga-Kruse cultures or toxin has a very potent antitoxic effect in animal experiments, and clinically a most favourable effect on the course of the human disease.

Sera have been prepared and used therapeutically for man by Rosenthal (1904), who used antitoxic sera prepared with Shiga-Kruse strains, with considerable success. Others have recorded equally satisfactory results (see Lüdke, 1911).

Ruffer and Willmore (1910) used polyvalent and monovalent sera prepared with strains of both groups, and record strikingly beneficial results.

We see, therefore, that pure cultures can be made to produce a serum which is curative for man, making the chain of evidence for the causal connection of the bacillus with human disease almost as complete as in the case of diphtheria and the *B. diphtheriae*.

5. Further evidence of the capability of the *B. dysenteriae* (Shiga) to produce dysentery is afforded by the experiment of Firth (1904), who fed an ape with pure culture, and produced a disease in this animal quite comparable to that found in man.

Moreover, the occurrence of spontaneous dysentery in monkeys associated with *B. dysenteriae* (Flexner) has been recorded by Bowman (1910).

III. OCCURRENCE IN THE BODY.

The *B. dysenteriae* does not invade the tissues and various parts of the body in the same way as the *B. typhosus ;* in fact, its occurrence is almost limited to the contents of the intestines and the intestinal mucosa and submucosa. It has occasionally been found in the mesenteric lymph glands, but seldom or never in the spleen, liver, gall-bladder, or urine.

Vincent (1908), moreover, made experiments on rabbits, in which he aimed at producing infection of the gall-bladder and urine, but his attempts were unsuccessful. Joints are sometimes affected in dysentery, and rarely a conjunctivitis occurs. The large intestine is the principal seat of the morbid processes which the *B. dysenteriae* excites, but the small intestine is often more or less affected.

Chronic ulcers often appear to be free from the specific bacillus, or, at any rate, cultures of the organism cannot be procured from these lesions. The culture-plates inoculated with material from chronic ulcers are usually overgrown with numerous other bacteria—*e.g.*, *B. proteus*, *B. pyocyaneus*, etc.

The *B. dysenteriae* is most readily isolated from the frequent small stools, consisting of blood and mucus, which are passed from ten to thirty times a day during the acute stage of the disease. In the mucus contained in these stools the bacilli often occur in very large numbers, and almost to the exclusion of other intestinal bacteria. Later, when the evacuations have again become fæcal, the bacilli are much less numerous, though if pellets or streaks of mucus or flakes of muco-pus can be found, an abundant culture can sometimes be obtained. When relapses occur, and the characteristic mucous stools return, the bacilli may be as numerous as at first. In the chronic stages of the disease, when pus occurs in the motions from the ulcerated surfaces, the bacilli are fewer, and frequently detection is rendered difficult by the secondary infecting organisms.

As the acute attack is passing off, about the eighth day, or earlier, the *B. dysenteriae* become fewer and the colonies on culture-plates of infrequent occurrence; but excretion of *B. dysenteriae* may continue for a much longer period.

Drigalski (1902), speaking of the Doeberitz epidemic which was associated with the Shiga-Kruse bacillus, states that, after five or six days of illness, it was difficult to demonstrate the *B. dysenteriae*. Cases of "catarrhal diarrhœa," which are common during epidemics of dysentery, are often in reality very mild attacks of this disease, and yield *B. dysenteriae* readily during the first few days, and may continue to do so long after apparent recovery. When the motions are solid, *B. dysenteriae* can sometimes be readily isolated from the mucus on the surface of the fæces.

The *B. dysenteriae* is usually found more abundantly in the stools when the infecting organism belongs to the Shiga-Kruse group than when bacilli of the mannite-fermenting type are responsible for the attack.

The proportion of clinical cases which yield the bacillus varies considerably in different epidemics and districts. Fischer, Hohn, and Stade (1910), in an epidemic at Essen, during which 96 cases of dysentery were reported, found evidence of infection by the Shiga-Kruse bacillus in 58. Much depends on the stage of the disease at which the examination is made.

Mayer (1910) investigated an outbreak in an infantry regiment at Fürth. He found a *B. dysenteriae* resembling the Flexner strain in 51 out of 53 cases of disease, in 27 out of 28 severe cases, and in 21 out of 23 cases of catarrhal diarrhœa. He also found 22 healthy carriers among 573 men; 73 persons were therefore found infected, or 12·7 per cent. of the whole force. The bacilli when found were almost always detected at the first examination —*i.e.*, during the acute stage.

Of the 53 patients who yielded bacilli 37 (70 per cent.) were well bacteriologically—*i.e.*, they had ceased to excrete bacilli in four weeks from the onset; 9 (31 per cent.) of the 28 severe cases continued to yield bacilli for five to sixteen weeks; 7 (28 per cent.) of the 25 catarrhal cases yielded *B. dysenteriae* for five to twelve weeks; 18 (81 per cent.) of the 22 healthy carriers yielded *B. dysenteriae* for one week only; 2 (9 per cent.) of the 22 healthy carriers yielded *B. dysenteriae* for two weeks; and 2 (9 per cent.) of the healthy carriers yielded *B. dysenteriae* for four weeks.

Severe cases appeared to "carry" for a longer period than mild cases and "healthy carriers." During convalescence the bacilli remain long after apparent return to health, and after the motions have resumed their natural appearance.

Conradi (1903) found patients with normal stools in whom the *B. dysenteriae* persisted two to four weeks.

Pfuhl (1902), in a severe case of dysentery, found the *B. dysenteriae* after four months. He thought every case of dysentery should be considered infectious for one to two weeks after the disappearance of symptoms.

Lentz (1907) found that 3 out of 12 cases of dysentery due to a mannite-fermenting strain continued to excrete the bacillus for four to five weeks after complete clinical recovery.

Mayer (1910) considers that on the average *B. dysenteriae* persists for two to three months after clinical recovery, but that four weeks' isolation is probably sufficient for healthy carriers. The examination may be negative for a long period, and then the bacilli reappear in the stools. An interval of as long as two months, during which the motions are apparently free from bacilli, may occur. When the bacilli reappear after long intervals, an attack of the nature of a relapse has usually supervened.

In this country similar results have been obtained in epidemics of asylum dysentery. Aveline, Boycott, and Macdonald (1908) found *B. Flexner* in 17 out of 19 cases of acute asylum dysentery, whereas 26 control cases (5 of which had diarrhœa) from the same wards all gave negative results.

5 cases were examined during convalescence.

1	was negative	13	days	after the attack.
1	,,	8	,,	,,
2	,,	14	,,	,,
2	,,	25	,,	,,

One case was examined two days before the onset of an attack, and then gave a negative result.

Macalister (1911) examined twenty-eight specimens of stools from acute cases of dysentery in an asylum, and in thirteen obtained a bacillus resembling Flexner's *B. dysenteriae*. The bacillus tended to disappear when the patients got well clinically, but the clinical convalescence preceded the disappearance of the bacilli.

In all, some 200 specimens of stools were examined from 120 patients.

Of those examined	during	1st week	of illness,	67	per cent.	gave a positive	result.
,,	,,	2nd ,,	,,	33	,,	,,	,,
,,	,,	3rd ,,	,,	25	,,	,,	,,
,,	,,	4th ,,	,,	16	,,	,,	,,
,,	after	2 months		20	,,	,,	,,
,,	,,	3 ,,		0	,,	,,	,,

Of those	examined	in the	1st week,	100	per cent.	were still suffering from a definite clinical attack.
,,	,,	,,	2nd ,,	23	,,	
,,	,,	,,	3rd ,,	8	,,	
,,	,,	,,	4th ,,	4	,,	
,,	,,	after	2 months	1	,,	
,,	,,	,,	3 ,,	0	,,	

The patients, therefore, appeared well before the disappearance of the bacilli—*e.g.*, during the fourth week 16 per cent. still yielded the *B. dysenteriae,* but only 4 per cent. were clinically still unwell.

Macalister estimated that probably 20 per cent. of these cases were infective for five weeks to two months. He found no "healthy carriers"—*i.e.,* carriers who had not been ill.

The cases of dysentery investigated in this epidemic were classified by Macalister under four headings, according to their history after the first acute attack.

	Males.	Females.	Total.	Percentage.
1. Complete recovery	20	23	43	53·0
2. Single attack. Stools continued to contain mucus; agglutination remained high	9	7	16	20·0
3. Relapsing cases	4	15	19 } 21	26·2
4. Chronic cases	—	2	2	

The second class were not shown to be carriers. The 26·2 per cent., consisting of the relapsing and chronic cases, formed the great proportion of those who continued to be dangerous, according to Macalister.

Rarely cases of sporadic dysentery and ulcerative colitis in this country have been shown to be infected with the *B. dysenteriae.*

Marshall (1909) published a fatal case of dysentery in a child, from which the *B. dysenteriae* (Flexner type) was isolated, but the source of infection was not conclusively established.

Hawkins (1909) published a case of dysentery in an adult from whom a mannite-fermenting *B. dysenteriae* was isolated. This man gave a history of relapses extending over at least five years, and he was no doubt in fair health at various periods during that time, although a carrier. The bacillus was not looked for till 1909.

Bainbridge and Dudfield (1911) gave details of an outbreak of diarrhœa affecting 12 children, 4 or more of whom had violent diarrhœa and passed much blood, and one other child had an indisposition of doubtful character.

A *B. dysenteriae* of the mannite-fermenting group was isolated from 4 patients. The length of time which had elapsed since the onset in 3 of the 4 cases was nineteen days, twenty-two days or thirteen days, and eleven days.

The blood serum of 3 patients agglutinated *B. Flexner* in a dilution of 1 in 100. The characters of the *B. dysenteriae* isolated were as follows:

It was agglutinated by 1 in 1,000 dilutions of immune sera obtained from rabbits inoculated with *B. Flexner* and *B. dysenteriae* "Y." The bacillus was non-motile and produced acid without gas from glucose, mannite, sorbite, arabinose and galactose, but not from lactose, cane-sugar, dulcite, maltose, or other carbohydrates which were used.

CARRIERS OF B. DYSENTERIAE.

Healthy Carriers.

1. "Healthy carriers" of the *B. dysenteriae* who have not had an acute attack either mild or severe, have been considered by many writers very rare. Kruse (1907) reported one such case. Duval and Bassett (1903) and Jehle and Charleton (1905) report the isolation of the *B. dysenteriae* (Flexner type) from 2 healthy children. Conradi (1903) reported the finding of *B. dysenteriae* (Shiga-Kruse) in 5 quite healthy children whose relations at the time were ill with dysentery. Ford (1903) isolated *B. dysenteriae* from the intestine in 10 out of 50 post-mortem examinations in cases of other diseases than dysentery. Wollstein (1903), on the other hand, made post-mortem examinations of 24 young children, and found "pseudodysentery" three times, but in all 3 of these children the intestine was inflamed and diarrhœa had occurred during life.

Of late years the occurrence of the bacillus has been frequently recorded in persons from whom no history of an attack resembling dysentery could be obtained.

Morgan (1911) describes certain strains of *B. dysenteriae* of the mannite-fermenting type, which were isolated by Ledingham from a number of persons whose stools were being examined for the *B. typhosus*, and who, so far as could be ascertained, were not known, except in one or two instances, to have had dysentery themselves or to have been in association with cases of dysentery. The characters of these strains and their significance are discussed on p. 275.

Mayer (1910) records 22 "healthy carriers" amongst 573 soldiers during an outbreak; also in the epidemic reported by Simon (1910), and mentioned at length below, 70 cases of dysentery occurred, and 86 " healthy carriers " were detected.

Precocious carriers must be mentioned, though there is little evidence that such cases occur often. By this term is meant persons who have been detected as healthy carriers without previous illness, and who later develop dysentery. One such case is given by Mayer. This patient developed bloody diarrhœa on the ninth day after isolation. It is obvious that such carriers can rarely be distinguished from very mild cases in which relapses have occurred.

The other varieties of dysentery carriers may be classified thus : (2) Convalescent ; (3) Relapsing ; and (4) Chronic.

Convalescent Carriers.

By convalescent carriers are meant those persons who, after an attack, continue to discharge the *B. dysenteriae* in the motions, although these appear natural at first sight, and all symptoms have ceased.

Kirchner (1908) gave as a rule that before a patient was released from isolation, two negative examinations at a week's interval should have been made.

Mayer (1910) found that this rule was insufficient. He calculated that if this rule had been followed 44·4 per cent. of his cases of dysentery, and 36·3 per cent. of his cases of intestinal catarrh associated with *B. dysenteriae* would have been released from isolation a long time before they were actually free from bacilli.

Mayer's rule, with regard to isolation, was that three to four negative examinations must be made in the course of the two to three weeks after the last positive result, before the isolation could be relaxed.

He gives an instance of a man who on March 1 had apparently yielded *B. dysenteriae* for the last time. Negative examinations were made on March 5, 10, and 14 ; on March 17 the *B. dysenteriae* was again found. He also records another case in which a convalescent was examined with negative results on February 26. Three negative results were then obtained, and he was released from isolation on March 11.

On March 29 he was again examined with a positive result, and two cases of dysentery occurred in the same company of soldiers as a sequence to his release from isolation.

Relapsing Carriers.

The following case of relapsing dysentery is described by the same writer: Four negative examinations of a convalescent soldier were made in the course of more than three weeks. He was then released. On March 26 he had a relapse, and on March 28 a fresh case of dysentery occurred in the same room in the barracks. About the same time, and in the same company, another case of dysentery and ten more carriers were found.

A recrudescence of the epidemic was probably due to this release of carriers at too early a date.

Drigalski (1902) says that relapses may occur after intervals of two to five months.

Kruse (1908) considers that relapsing cases constitute a very dangerous source of infection, and that they are probably as infectious—*i.e.*, excrete as many bacilli—as the early primary cases. He also thinks that patients who suffer from relapses are apt to be more careless, and therefore a more potent cause of mischief. He mentions the case of a man in whom relapses had occurred two years after his original attack of dysentery.

The *B. dysenteriae* was readily isolated during one of this man's relapses. Kruse does not consider carriers in apparent health to be very dangerous, because he is of opinion that these cases do not excrete many bacilli.

Chronic Carriers.

Chronic, as distinguished from relapsing, cases of dysentery are considered by Kruse (1908) to be of comparatively little danger to the community, as the *B. dysenteriae* excreted are usually few in number, having been outgrown by other bacteria which are present in the pus from chronic ulcers.

With regard to the spread of the disease during an epidemic, or its importation during the epidemic season from one town or district to another, probably the mild catarrhal cases, the convalescent carriers, and cases relapsing at short intervals, are the most active. But in determining the survival of the *B. dysenteriae* from one epidemic to another, the relapsing and chronic cases of dysentery must be regarded as the chief factors. If, however, observations like those of Simon (1910) are repeated and confirmed, the chronic (convalescent) carrier assumes a still more important position.

The accepted views as to the persistence of *B. dysenteriae* in persons who have once been infected, have of late years been materially altered. Extended observations have shown that the bacillus continues to be excreted by persons apparently in health for much longer periods than was formerly supposed.

Simon (1910) records the results of examination during the first seven months of 1909 of the soldiers stationed at Hagenau, near Strassburg, who were infected during the summer of 1908. The variety of *B. dysenteriae* found during this epidemic was that known as *B.* "Y."

Of the men who were attacked or found to be carriers in the summer of 1908, 154 were still available for re-examination in January, 1909. Seventy of these had suffered from an attack of dysentery, and 84 had been shown to be infected as "healthy carriers." From only 55 of the 70 cases of dysentery was the *B. dysenteriae* isolated in 1908, and the remaining 15 still gave negative results in 1909. However, 4 (*i.e.*, 5·7 per cent.) of the 70 soldiers who suffered from dysentery in 1908 were found to be carriers in 1909.

The patients had all been discharged from isolation at least three months before the re-examination took place, and they had yielded three negative results before they were released.

These cases of prolonged persistence of the bacillus are so important that some details as to the findings in these four cases will be given :

	Case 1.	Case 2.	Case 3.	Case 4.
Last positive examination (1908)	Aug. 17	Oct. 21	Sep. 1	Aug. 3
Date of first re-examination (1909)	Jan. 20	Jan. 19	Jan. 19	Jan. 18
Number of re-examinations (1909)	24	7	10	11
,, positive results (1909)	11	1	1	1
,, re-examinations (1910)	8	—	—	—
,, positive results (1910)	1	—	—	—
Date of last positive result ..	Ap. 12, '10	Jan. 19, '09	Jan. 19, '09	Jan. 19, '09
Total period of persistence ..	618 days	162 days	144 days	214 days

Of these persistent carriers, two were originally abortive cases and two slight cases.

The number of bacilli present in the stools of the chronic carriers was not usually very large. On Conradi-Drigalski plates the colonies of *B. dysenteriae* were as a rule very few in number, and only occasionally could they be called numerous. They never formed the overwhelming majority of the colonies present, as often happens in the case of typhoid carriers.

The re-examination of the 84 "healthy carriers" found in 1908 yielded still more remarkable results.

From 13 (15·4 per cent.) the *B. dysenteriae* was isolated in 1909, showing a much larger proportion of persistent carriers than was found amongst the clinically more important cases.

The ascertained persistence of the bacillus in these 13 men varied from 137 to 404 days, with an average of 214 days. The chronic carriers who remained over from this epidemic for more than three months amounted altogether to 11 per cent. of those attacked or recognized as being infected during the previous year; and the existence of a probable connection by means of carriers was established sufficiently to account for outbreaks in successive years or even at longer intervals.

Simon remarks that during this investigation the positive results were more frequently obtained during the colder weather. He attributes this either to the harmful effect of the cold on the men or to the better preservation of the specimens of fæces which were sent from Hagenau to Strassburg for examination.

The cases of mild attack or catarrhal diarrhœa are very important in epidemics. Fischer (1910) draws special attention to them. He thinks that during the epidemic at Essen, which he investigated, the children were largely concerned in the spread of the epidemic. Half the cases were under fifteen years, and he came to the conclusion that many cases among children were mild and not notified. Fischer also points out the likelihood of direct spread of the disease amongst children playing together in the streets, especially in very poverty-stricken and ill-scavenged districts.

The original chronic case or carrier from which an epidemic starts has seldom been detected with any degree of certainty. Occasionally a person who has been associated with dysentery is found in the centre of a fresh epidemic focus.

Such a case is recorded by Fischer (1910). A secondary epidemic occurred in a street some distance away from the previous outbreak, and was apparently due to a woman who came from the primary area to visit her daughter-in-law. The mother-in-law was not shown to be a carrier, but her serum in high dilutions agglutinated the *B. dysenteriae* (Shiga-Kruse), which was the organism found in this epidemic.

The agglutinating activity of a patient's serum after a few days of illness begins to rise till it reacts with the bacillus in a dilution of 1 in 50 to 1 in 1,000, in the case of the Shiga-Kruse bacilli, or 1 in 100 to 1 in 500 when the infection is due to the Flexner group. Agglutination usually occurs in one hour at 37° C.

The agglutinating power soon sinks during convalescence. The fall begins generally after two or three weeks from the onset, but relapses may revive the diminished activity. Thus healthy persons whose serum agglutinates *B. dysenteriae* (Shiga-Kruse) in a dilution of 1 in 50, or *B. Flexner* in 1 in 100, should be regarded as suspects, and have probably recently been carriers, even if they are not still infected with the bacillus.

Macalister (1910)* found, in the course of an asylum investigation, that the serum of several patients continued to agglutinate the *B. dysenteriae* (Flexner) for two or three years after the first and last attack of dysentery which had been observed. In one case, eight years after the only attack recorded, the patient's serum agglutinated the bacillus completely in a dilution of 1 in 200 and partially in 1 in 400. In another case only one attack had occurred five years before, but complete agglutination occurred in a dilution of 1 in 400. In a case in which relapses had occurred four and a half, four, and three years before, but not more recently, the agglutination was complete in a dilution of 1 in 100 of the patient's serum.

In all these cases the *B. dysenteriae* was not isolated, but in most of them only one specimen of the stools could be procured. This failure to detect the bacillus does not, therefore, much detract from the probability that the bacillus was still present in the patient's intestinal tract.

IV. INFECTIVITY, AND MEANS OF DISSEMINATION.

The degree of infectivity of cases of dysentery depends on the numbers in which the specific organisms are present in the stools and the frequency with which the stools are passed. The danger of the infected person to others is diminished, or confined to a narrower circle, if the patient remains in bed ; but if, on the other hand, he is so situated that he uses a closet which is also used by many other persons, the risk of his infecting others is far greater. In cases of dysentery occurring under such circumstances, not only do the clothes become soiled, but the floor and surroundings of the closet are also liable to become infected. In crowded and poor districts, danger from these sources is of course much greater, especially where the sanitary arrangements are primitive and insufficient.

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* And in unpublished observations verbally communicated to the writer.

Fischer (1910) gives a vivid description of the unsatisfactory sanitation in the poor districts of Essen, where ninety-six notified cases, and probably more of a milder type, occurred in 1909. In such districts the dissemination of infection will be readily understood.

Probably the most frequent way by which the disease is spread is by direct contact with persons (patients or carriers) who are discharging large numbers of the bacilli, or with articles contaminated by them.

Amongst such articles besides clothes, etc., mentioned above, are food, such as fruit and vegetables, which are sold on barrows and in shops, and are often handled by many persons, as pointed out by Fischer. Cooks and all persons who help in preparing food are probably efficient agents in the spread of the disease.

When the soil is grossly contaminated, flies and dust may readily serve to infect food and water, and it is to be especially noted that the season of greatest prevalence is the summer, when flies are most numerous, and also drought and dust are apt to occur.

A water-supply has seldom been incriminated, for though, as in Essen, the *B. dysenteriae* may be occasionally isolated from a sample of water, still the epidemic rarely increases in an explosive manner, and the disease is apt to spare the wealthier and less crowded parts of a town, even when the water-supply is identical in the two districts.

Special articles of food have been accused of being the source of infection, as in the epidemic recorded by Mayer (1910) when a special article of diet, " Tierleber," was suspected. No support for this suggestion was obtained by examination of the food in question.

The *B. dysenteriae* does not live well outside the body, being readily overpowered by other bacteria. Most experimenters

(Lentz, 1909) have only noted a survival of a few days on unsterilized materials. In all cases in which dust, water, or food, is suspected of causing infection, the real source of the bacillus is almost certainly, therefore, a human being, since lower animals are not known to be naturally invaded by the *B. dysenteriae.* The spontaneous occurrence of bacillary dysentery in monkeys has been, however, recorded by Bowman (1910) in the Philippines.

Treatment of Carriers and Prophylaxis.

The treatment of carriers resolves itself into the use of appropriate remedies for the diseased mucous membrane of the intestine, which is assumed to exist in carriers. In some chronic cases the direct application of caustic remedies to the ulcers has, with the aid of the rectoscope, been practised with some success.

The prophylactic measures directed against carriers include isolation of convalescents till the stools have given three negative results at intervals of a week, the examination of contacts and other persons in the near neighbourhood for the presence of the *B. dysenteriae,* and the isolation of such carriers for a similar period.

When isolation is impossible, strict rules of cleanliness must be inculcated, and infected persons must be prevented from handling food.

Great care must be taken to protect the excreta from flies, and to disinfect them or so dispose of them that they shall be innocuous.

A close watch should be kept over persons who have once been infected, and any attack of diarrhœa occurring in a formerly infected person must be considered suspicious, and calls for re-examination.

On the occurrence of a fresh outbreak of dysentery those who have formerly been infected must be re-examined.

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CHAPTER VII

CHOLERA

I. INTRODUCTION.

THE comma bacillus was originally described by Koch as the result of his researches during the Egyptian epidemic in 1883, and it was then declared by him to be the causal organism of Asiatic cholera. At that time the most striking facts ascertained were the constant presence of the bacillus in enormous numbers in the stools of those suffering from cholera as opposed to those who had other diseases or who were in health.

Cultural methods had been very much improved, when the opportunity occurred, during the European epidemics of 1892-1896, for further thorough investigation of the disease.

It was then found that in the numerous mild cases of diarrhœa, which had long been known to occur in cholera epidemics, there was really infection with the specific cholera vibrio, and, moreover, that persons apparently in perfect health, but associated with cases of cholera, were similarly invaded with the same organism. It was also established that convalescents continued to excrete cholera vibrios after apparent return to health, but for a long time it was thought that the comma bacillus was never retained in the intestine for more than a few days.

Pfeiffer (1908) stated, as an important axiom, that true chronic carriers never occurred in cholera as they do in typhoid fever. This opinion may still be accepted as true, since the reverse has yet to be proved, although improved methods of examination have shown that in about one-third to one-half of the cases which recover, the cholera vibrio may be detected for more than ten days. Persistence for over a month is very exceptional. As a rule, in mild cases and convalescents the number of vibrios is comparatively small. Pathological researches have shown that the cholera vibrio is not found in the tissues of any organ except the walls of the intestine, and as a rule not deeper than the mucosa. Probably the occasional successful cultivation from the liver, kidney, etc., is only the result of invasion of the blood-stream just before death.

In the German outbreaks, the introduction of cholera was on several occasions traced to persons from infected areas who themselves remained in good health—*e.g.*, in the case of the Hamburg epidemic.

It is, however, doubtful how far so-called " healthy carriers " have really been healthy throughout ; probably nearly all have had slight symptoms at some time.

Many epidemics of cholera have undoubtedly been due to an infected water-supply. This was strikingly the case in the Hamburg epidemic of 1892, in which the line of separation between the healthy town of Altona and the heavily attacked town of Hamburg was the division between two districts which corresponded to no natural boundary, and, in fact, often ran along the middle of a street, the essential distinction being the different water-supply.

Janssen (1910) described the course of an outbreak which took place in 1909 in six separate centres in Gumbinnen in East Prussia. Each new centre was apparently infected by the inhabitants of boats which came down the river from Russia, or possibly by the river water itself. Subsequent spread took place by contact.

Thirty-three infections in all occurred, of which eight (24·2 per cent.) were fatal. In each centre the severity of the attacks became gradually less, and the decline of each outbreak was characterized by the presence of carriers only.

This observation of declining severity of the cases during the progress of the outbreak suggests that the later carriers were not effectual in producing disease, either by a decline in the virulence of the vibrios which they harboured, or by the smallness of the numbers of vibrios which they excreted.

The former supposition has not been established by experimental observations, but the question of mutation amongst cholera vibrios is not yet settled. This subject will be further discussed in Section II.

II. BACTERIAL DIAGNOSIS.

Certain types of acute diarrhœa not due to infection with Koch's vibrio may simulate Asiatic cholera clinically. Bacteriological aid is essential, therefore, not only in order to decide at the commencement of an epidemic the true character of the disease present, but also to determine how long convalescent patients continue to be infective, to make a diagnosis in mild and abortive cases, and to detect "healthy carriers."

MATERIAL FOR EXAMINATION.

The material in which the cholera vibrios should be sought is confined to the intestinal contents and evacuations. The stools must be collected in vessels which have been, if possible, sterilized, and at any rate not merely washed out with unboiled water, which is liable to contain saprophytic vibrios.

At the port of New York in the summer of 1911 each passenger on ships from infected ports was examined by passing a sterile swab on a wire handle into the rectum, and using this to inoculate a culture medium consisting of peptone-water. By this means about 1 per cent. of apparently healthy passengers who were examined were shown to harbour the vibrio of Koch.

In the case of post-mortem examinations samples of the intestinal contents must be taken from the small intestine, especially from the lowest portion of the ileum.

BACTERIOLOGICAL DIAGNOSIS.

The essential bacteriological methods by which the cholera vibrios are detected and identified in patients and carriers are the following:

1. Direct microscopic examination of the stools for vibrios.
2. Direct culture of the stools on a selective alkaline blood-agar in Petri dishes.
3. Enrichment by culture on alkaline peptone-water and subsequent plating.
4. Microscopic examination of the cultures for vibrios.
5. Agglutination of the vibrios in the peptone-water cultures, and also after isolation.

The best material in which to find the cholera vibrio is a typical rice-water stool during the acute stage of the disease. Formed motions during convalescence and in carriers, even when infected, do not as a rule contain nearly such large numbers of the vibrios. The method of culture is the following:

1. A flake or loop of the stool is plated on Dieudonné's alkaline blood-agar and examined for characteristic colonies in eight to twenty-four hours.

2. A loopful of the material is inoculated into a tube of alkaline peptone-water, and 1 c.c. is also put into 50 c.c. of alkaline peptone-water. The cultures are incubated at 37° C. After six hours a loopful from the surface of the peptone-water is examined both in a hanging drop and as a stained film. If motile vibrios are present a preliminary agglutination test with a potent agglutinating serum can be made in a hanging drop. A loopful from the surface is also plated on agar, or if only few or no vibrios are seen a subculture may be made to a second tube of alkaline peptone-water, which is in turn examined after six or eight hours.

3. The Dieudonné plates must be examined after eighteen to twenty-four hours, and suspicious colonies examined as to the morphology of the micro-organism, and tested for agglutination by making an emulsion from each of several colonies on a cover-slip with a drop of specific serum suitably diluted. An agglutinating serum, with a titre of at least 1 in 2,000, should be used. If a dilution of 1 in 1,000 of such a serum causes decided agglutination in one hour at 37° C., the test may be considered positive, but controls with normal serum and with salt solution must always be put up at the same time.

After isolation it is an advantage to further test the agglutination macroscopically in varying dilutions. Vibrios allied to the true cholera vibrio may occasionally be agglutinated in a dilution of 1 in 500.

Besides the above tests, cultures should be made on gelatine to test the liquefying properties of the bacillus. Complement fixation may be used as a confirmary test of doubtful strains. This last method has been used as a means of diagnosis before isolation of the bacillus. Antigen for this purpose is prepared from an emulsion obtained by washing off the growth from the plates. This is then tested in a hæmolytic system with a specific immune serum.

Pfeiffer's reaction and the pathogenicity or toxicity of cultures for laboratory animals are sometimes of special value for the examination of particular strains. The development of hæmotoxin, which dissolves red-blood corpuscles in emulsion, has also been much used as a means of differentiation, but is probably of little value.

Preparation of Culture Media.

The peptone-water for enrichment is best prepared (Kolle and Schürmann, 1911) by making up a stock solution, as follows:

Peptone (Witte)	100 grammes.
Sodium chloride	100 ,,
Potassium nitrate	1 gramme.
Crystals of carbonate of soda	2 grammes.
Distilled water	1 litre.

For use, the above must be diluted 1 to 9 with sterile distilled water, put in tubes each containing 10 c.c., and again sterilized.

The alkaline blood-agar recommended by Dieudonné (1909) is prepared as follows:

Normal potassium hydrate	equal parts.
Defibrinated ox blood	

Mix, and sterilize by steam. Add 30 parts to 70 parts of nutrient agar. Mix, and pour into plates, which must be kept at least twenty-four hours before use, and should be dried slightly.

Pilon (1911) introduced a modification of Dieudonné's medium which can be used at once. His formula is:

Defibrinated blood (pig's, goat's, or rabbit's)	equal parts, not sterilized.
12 per cent. solution of crystalline sodium carbonate	

Add 3 parts to 7 parts of 4 per cent. neutral agar; mix; pour into plates.

A selective alkaline blood-agar has this advantage over agar or gelatine, that a larger amount of the material to be examined can be spread on each plate without the colonies of vibrios being overgrown by other bacteria which are inhibited by this medium.

MacLaughlin and Whitmore (1910), however, did not find Dieudonné's medium of any use for separating true from false cholera vibrios.

This method may save time in obtaining pure cultures of the *Vibrio cholerae*, but it has the disadvantage that a certain proportion of failures to isolate the vibrio occur, and that colonies which appear pure are apt to prove contaminated by *Bacillus coli* when subcultured on to ordinary agar or peptone-water, on account of the inhibition of the latter organism by the alkaline medium, and its reappearance when transplanted to a neutral medium.

Tanda (1911) examined 107 cases of cholera by both peptone-water enrichment and direct plating on Dieudonné's medium. In 5 cases which were approaching recovery he obtained no growth on "Dieudonné," but a positive result with peptone-water.

Tuchinski (1910) found that 10 per cent. of the rice-water stools examined with Dieudonné's medium gave negative results.

Enrichment with alkaline peptone-water has the advantage that the vibrio may be obtained in a larger proportion of specimens ; but usually a longer time must elapse before a pure culture is obtained (about thirty to thirty-six hours at least), and most observers are of opinion that this method also enriches the saprophytic vibrios (Kolle and Schürmann, 1911). Krumwiede (1910), however, states that he did not find the ordinary water vibrios enriched by peptone-water.

Variant Strains.

In some epidemics it is possible to obtain the specific vibrio from the stools of cholera patients with great regularity, and at the same time the cultural and serological properties of the strains isolated show a striking uniformity.

This was exemplified in the epidemic at Marseilles in which Orticoni (1911) found only three aberrant vibrios, which were isolated from choleraic patients. These three strains did not agglutinate nor give Pfeiffer's reaction with an anticholera serum.

Most writers, especially German, Italian, and American, consider that agglutination nearly to the limit of the titre with a potent agglutinating serum is diagnostic. Low agglutinability, however, cannot in all cases be looked upon as conclusive evidence against the specific nature of the organism isolated from cases of the disease, unless this character persists on subculture. For practical purposes agglutinability must be considered as the criterion in the examination of suspected carriers.

MacLaughlin and Whitmore (1910) in the Philippines found some cholera-like vibrios in cholera suspects, but none agglutinated with a greater dilution of specific serum than 1 in 10.

Four strains, however, regarded by them as true cholera vibrios, were obtained, which were agglutinated unequally by the four sera prepared with them. This experience appears to indicate some variability in agglutinating properties even in true cholera strains.

During some epidemics vibrios may be found in patients, and also in river and harbour water, which resemble the cholera vibrio in morphology and cultural characters, but which do not agglutinate with high dilutions of cholera serum. When this is the case, these strains do not react to Pfeiffer's test. By far the most important test for distinguishing the vibrios is the agglutination, in spite of these exceptional occurrences.

Some investigators have maintained that cholera vibrios may very readily be made to undergo variation, so that they no longer agglutinate in high dilutions nor react to Pfeiffer's test with immune serum, and show divergence in other cultural characters. One of the methods which have been employed to bring about these changes is keeping the vibrios in sterile water, and it has also been claimed that vibrios which commonly occur in river or harbour water, and which, when first isolated, differ in most respects from true cholera vibrios, especially in their serum reactions, can, by suitable cultural or other means, be so altered as to agglutinate and in every way behave just like true cholera vibrios.

The chief advocates of these mutation phenomena are Horowitz (1911) and Zlatogoroff (1911), who have worked at St. Petersburg with cultures obtained in Russia.

Zlatogoroff gives detailed descriptions of several methods, including animal passage and re-isolation at different periods after infection, by which the vibrios may be notably changed in their serum reactions. Zlatogoroff also maintains that vibrios isolated at the same time from the same guinea-pig have very different agglutinability, according to whether they are isolated from the peritoneal fluid, blood, or liver. He also states that the vibrios become altered in their morphology, in the appearance of their colonies on gelatine plates, and in their agglutinability during the course of the disease in man, the agglutinability diminishing as the disease advances.

The occurrence of these changes has been recently investigated thoroughly by Wankel (1912), who obtained cultures of these cholera-like vibrios from Horowitz, and repeated the experiments. He also used an undoubtedly true strain of cholera vibrio and attempted to produce variation by the methods described by Zlatogoroff. Wankel completely failed to obtain any evidence of variability either with the cholera-like water vibrios or with true cholera bacilli.

For the present, therefore, the claim that non-pathogenic vibrios frequently undergo mutation, so as to become indistinguishable from true cholera vibrios, or *vice versa*, may be put on one side as unconfirmed and improbable.

An extremely interesting and important strain of cholera vibrio was found at El Tor in pilgrims coming from Mecca, by Ruffer and Gotschlich, who described the vibrios in detail. Gotschlich (1906) isolated this race from the bodies of five pilgrims examined post mortem. At first it was thought that the strain showed characters which differentiated it from the true vibrio of Koch, although it reacted specifically as regards agglutination and Pfeiffer's test. Markl (1906) maintained that by complement fixation experiments he could distinguish between the two organisms. The production of hæmotoxin and certain other peculiarities, including a high toxicity, were also claimed as special features of the El Tor strain. However, the researches of Kraus (1902), Kolle and Gotschlich (1903), Kolle and Meinicke (1905), and Neufeld and Haendel (1907) have shown that these differences are of no importance.

It is now, therefore, generally accepted that the El Tor strain is a true cholera vibrio. The interesting fact in connection with this strain was that it occurred in pilgrims who had not shown the symptoms of cholera. Moreover, no cases of this disease had occurred for some time in Arabia. These carriers, however, came from Asiatic Turkey and Russia, countries in which cholera was then (1904-05) epidemic, though the time since their departure from home must have been many weeks. Ruffer suggested that they had obtained the vibrio from certain pools of filthy water in Mecca, in which case only about six weeks might have elapsed since they first became invaded.

The discovery of genuine cholera vibrios in healthy persons at El Tor in the circumstances mentioned above appeared much more remarkable at that date than a similar observation would do at the present time. In the last few years various pathogenic bacteria have been frequently shown to invade healthy persons, and to prolong their sojourn for weeks or months. Although persons infected with the cholera vibrio generally do not "carry" this micro-organism for more than a few days or weeks, still much longer periods of invasion have been reported.

VIABILITY OF CHOLERA VIBRIOS.

It has been shown by many observers that the cholera vibrio is very readily destroyed by drying. It is therefore extremely improbable that dust or dry materials are a frequent means of disseminating this organism.

The infection may, however, be direct through articles recently soiled by infected evacuations. On the other hand, the vibrio lives well in water, as is the case with other known vibrios.

Several experimenters have shown that cholera vibrios can live for many days in water, and their disappearance is due apparently to their being crowded out by the activity of other bacteria.

The bacteria occurring in water are so variable in different samples that the survival of cholera vibrios must vary very much if dependent on the other bacteria present. In many of the recent epidemics in Europe—*e.g.*, those in Italy in 1910-11, and at Marseilles in 1911—the infection appears to have been due chiefly to contact between convalescents or carriers and the healthy.

Dunbar (1894) found that in water from Hamburg harbour the cholera bacillus lived sixteen to twenty-five days.

Jacobsen (1910) obtained Koch's vibrio from a sample of harbour water forty-seven days after a culture had been put in it.

Zlatogoroff (1911) placed twenty-eight samples of cholera stools in bottles and kept one set of bottles at 16° to 18° C. and another at 3° to 8° C. He recognized the cholera vibrio after forty-seven days, when the material was kept in frequently-opened bottles at 16° to 18° C., and after seventy-eight days when kept at 3° to 8° C. In other bottles which were kept hermetically sealed, and only opened once, the vibrios persisted six and a half months at 16° to 18° C., and seven months at 3° to 8° C.

These and numerous other experiments show that water and the cholera stools themselves are probably the chief means of preserving the vibrio outside the human body.

III. THE OCCURRENCE AND DISTRIBUTION OF CHOLERA VIBRIOS.

As a rule, the vibrios are not found in human organs or tissues other than the intestinal contents and mucosa. Probably the occasional presence of the bacillus in the blood and kidney post mortem is due to an invasion during the last hours of life. Pathological changes due to the presence of the bacilli are not found in any tissues except the mucous membrane of the intestine.

The parenchymatous changes in the kidney are no doubt due to poisoning by toxin formed in the intestine.

Kulescha (1910), by means of peptone-water enrichment, recovered the cholera vibrio constantly from the bile post mortem, and describes inflammatory changes in the gall-bladder in 10 per cent. of the cases examined. It is practically always possible to cultivate cholera vibrios post mortem from the mucous membrane of the small intestine in typical cases of cholera asiatica, or from the stools during life.

CONVALESCENTS.

During the epidemic in Germany in 1892 it was found that the cholera vibrios could be isolated from the stools of convalescents after apparent recovery. Guttmann (1892) found in a small number of cases that the vibrios could be detected in the stools at dates varying from the 5th to the 10th day of illness. This observation was repeatedly confirmed, but chronic carriers in whom the vibrios persisted for months or years were not discovered.

It was noticed early in the 1892 epidemic that "healthy carriers" were not uncommon. These were generally very slight cases which were not considered to resemble cholera clinically.

Friedheim (quoted by Pfeiffer, 1908) during the presence of cholera in Germany in 1893-94, found the cholera vibrio in 297 persons, of whom 51 were apparently in good health and were passing formed motions.

Abel and Claussen (1895) reported that 17 persons who suffered from very slight symptoms were infected with cholera vibrios, thus pointing out the true nature of these mild attacks, and establishing a connection between healthy carriers and severe clinical cases.

Frosch (1895) examined 42 infected persons and classified 16 (38 per cent.) of them as carriers (12 children and 4 adults). Of the remainder, 8 died, and 18 more were recognized clinically as cases of cholera.

Pfeiffer (1908) records that in a family of 10 persons 9 were infected, 4 died of cholera, 2 were slightly ill, and 3 were carriers.

He also mentions an epidemic in 1905, in which 174 cases of cholera occurred, and 38 carriers—*i.e.*, 18 per cent. of the total number of infected persons—were discovered.

MacLaughlin (1911) found 17 carriers amongst 268 healthy persons in Manilla in 1908.

Orticoni (1911), during the Marseilles epidemic in 1911, used the combined methods of enrichment in peptone-water and subsequent plating on Dieudonné's medium. He says that he could usually obtain a pure culture in sixteen hours.

In a lunatic asylum which he examined, he found that as a rule about 2·5 to 3 per cent. of the inmates in the various wards were "healthy carriers"; but in one part of the asylum, where the water-supply was contaminated, he found that 20 per cent. were carriers.

From all these and many other records it is clear that carriers occur amongst those who have not suffered from definite attacks of cholera, and although the majority of these persons have had mild attacks of diarrhœa, it is probable that some have had no noticeable disturbance of health.

PERSISTENCE.

The most important objects to be aimed at by systematic bacteriological examination during an epidemic are—(1) The discovery of unsuspected "healthy carriers"; and (2) the determination of the length of time during which the vibrio persists in infected persons.

In the earlier epidemics which were investigated bacteriologically, the duration of the infection was supposed to be very short. The failure to recognize instances of longer persistence was no doubt in part due to the fact that the method of enrichment with peptone-water was not systematically practised.

Guttmann (1892) examined ten convalescents, and found that the cholera vibrios were still present up to—

5	days in	3	cases.
7	,,	2	,,
8	,,	2	,,
9	,,	2	,,
10	,,	1	case.

Simonds (1892), from examination of cholera cases post mortem, determined that the cholera vibrio was always found up to the sixth day of illness. In half of his cases vibrios were present up to the twelfth day. Exceptionally, the persistence continued over twelve days, and once till the eighteenth day.

Rumpel (1894), in 117 typical cases of cholera examined during life, never found the vibrio after twenty-four days. In slight cases or "healthy carriers" the vibrio disappeared at latest between the eighteenth and twentieth day.

Rommelaere (1892) cultivated cholera vibrios in one case from stools passed on the forty-seventh day from the onset of the disease.

Pfeiffer (1908) gives some results of examinations during the epidemic in 1905. Whilst 174 decided cases of illness associated with vibrios occurred, 38 "healthy carriers" were detected. In the carriers, the vibrios as a rule were present for only a short time, and did not remain so long as in convalescents.

Each fresh epidemic now leads to extensive and careful examination of large numbers of cholera convalescents and "contacts." These investigations have furnished much the same results as those conducted during former outbreaks, except that the tendency has been to extend the time during which persons once infected remain carriers. There has been no confirmation so far of the observation of Janssen (1910), that the vibrio may persist in exceptional cases for over a year.

Zlatogoroff (1911) states that Jakowleff found cholera vibrios in a convalescent after fifty-six days, and that Zeidler records a similar observation in which the infection extended to ninety-three days.

He refers to the history of 324 cholera patients in a hospital at St. Petersburg, of whom 64 died; the fæces of 255 persons were examined bacteriologically by the method of peptone enrichment and subsequent plating on agar. The examinations were carried on from the first day of the disease till the vibrios ceased to appear in the cultures—*i.e.*, till the results had been negative for three days. After thirty-seven days all these

In	14	cases	the vibrios	persisted in	the stools for	4	days.
,,	28	,,	,,	,,	,,	8	,,
,,	4	,,	,,	,,	,,	10	,,
,,	29	,,	,,	,,	,,	12	,,
,,	59	,,	,,	,,	,,	14	,,
,,	73	,,	,,	,,	,,	17	,,
,,	26	,,	,,	,,	,,	21	,,
,,	5	,,	,,	,,	,,	22	,,
,,	7	,,	,,	,,	,,	27	,,
,,	2	,,	,,	,,	,,	32	,,
,,	2	,,	,,	,,	,,	33	,,
,,	1	,,	,,	,,	,,	37	,,
,,	2	,,	,,	,,	,,	42	,,
,,	1	,,	,,	,,	,,	48	,,
,,	1	,,	,,	,,	,,	51	,,
,,	1	,,	,,	,,	,,	56	,,

persons had formed stools; at least five cases, with solid motions, still yielded cholera bacilli. It is seen that in 180 persons (*i. e.*, more than 70 per cent.) the cholera bacillus was found up to the fourteenth day.

Kulescha (1910) and Bruloff and Tchiknaveroff have shown, according to Zlatogoroff (1911), that cholera vibrios are sometimes present in the gall-bladder and bile-ducts for a long time, although the liver and the intestine appear to be normal. These observations suggest that the intestine may be reinfected from the gall-bladder. As the blood is not known to be infected, probably the gall-bladder becomes infected through the bile-duct.

In the same epidemic in St. Petersburg, cholera vibrios were found by Filoff up to the hundred and first day, and by Kulescha for nine months (quoted by Zlatogoroff, 1911).

Janssen (1910) came to the conclusion that the length of time during which the vibrios were excreted by persons recovering from cholera had no relation whatever to the severity of the disease.

He records one case which had recovered clinically by the fifty-third day. From this patient vibrios were obtained up to the three hundred and sixty-ninth day. In "healthy carriers," on the other hand, he found instances in which the excretion of bacilli lasted two, four, five, six, and eleven days.

Tanda (1911), of Molfetta in Apulia, found that out of 50 patients—

15	(30	per cent.)	retained	the vibrio	for over 10 days from the onset.
5	(10	,,)	,,	,,	between 10 and 20 days from the onset.
6	(12	,,)	,,	,,	,, 20 ,, 30 ,, ,,
4	(8	,,)	,,	,,	over 30 days from the onset.

These last four cases retained the bacillus for thirty-one, thirty-four, forty-seven, and fifty-eight days respectively from the onset. He found that one or two intermissions often occurred in the series of positive results.

To some of his cases, after negative examinations had been made, Tanda administered magnesium sulphate in order to ascertain whether the vibrios would reappear in the diarrhœic stools which resulted. Twenty-five cases were examined in this way, after two or three negative results had been obtained with five-day intervals.

Three cases out of the twenty-five yielded cholera vibrios again after the aperient.

1. A boy, in whose case a few vibrios were obtained by these means forty-seven days from onset of the disease and forty-two days from the date of clinical recovery.

2. Cholera vibrios appeared after magnesium sulphate, fifty-six days from the onset of the illness.

3. After the vibrios had been obtained for sixteen days three negative results followed. Thirteen days from the last positive examination, the aperient was administered and cholera vibrios reappeared. Two further positive examinations came next, followed by two negative, after which the patient was discharged.

MacLaughlin (1911), in the Philippines, found no cholera carriers who could be shown to retain the vibrios for more than twenty days. No "latent cholera," nor cases with long incubation, were discovered.

Montefusco (1911) examined 107 cholera convalescents in order to ascertain the persistence of the cholera vibrio. He considered that freedom from the organsim had been established when three examinations of the fæces with one-day intervals gave negative results.

Vibrios were obtained for the last time—

In	11	convalescents	(10 per cent.)	on the	7th to 10th days.
,,	49	,,	(45·7 ,,)	,,	10th ,, 15th ,,
,,	23	,,	(21·4 ,,)	,,	15th ,, 20th ,,
,,	11	,,	(10·2 ,,)	,,	20th ,, 25th ,,
,,	6	,,	(5·6 ,,)	,,	25th ,, 30th day.
,,	2	,,	.. .. ..	,,	35th ,,
,,	1	,,	.. .. ..	,,	38th ,,
,,	1	,,	.. .. ..	,,	40th ,,
,,	1	,,	.. .. ..	,,	56th ,,
,,	1	,,	.. .. ..	,,	57th ,,
,,	1	,,	.. .. ..	,,	78th ,,

From these observations it is seen that about half of the persons who recover from a definite attack of cholera retain the vibrios for from ten days to a fortnight, whilst only 5 or 6 per cent. remain infective for over twenty-five days; but that amongst these latter 1 or 2 per cent. continue to excrete the bacillus intermittently for two or three months.

IV. PREVENTION.

Regulations drawn up with a view to preventing the occurrence of cholera in a country or town were formerly directed solely towards preventing persons who were suffering from cholera, or who were passing through the incubation stage, from entering that country or place. Attempts have been made to draw a cordon round an infected area, and a long quarantine for ships was formerly practised by many countries.

Koch, in his anticholera campaign in 1892, laid stress on the efficacy of slight cases and carriers in spreading the disease, in addition to the importance of drinking-water as a means of spreading cholera.

Since convalescents may retain cholera vibrios for forty-eight or even sixty days or more after recovery, a quarantine of any practicable duration would not insure a bacteriological cure of convalescents, and healthy carriers would be quite undiscovered unless a systematic bacteriological examination were carried out. Moreover, the intermissions in excretion of vibrios make a single negative examination by no means conclusive.

An attempt to set up a strict quarantine for ships from infected ports has so serious an effect on trade that energetic attempts to evade the regulations are inevitable.

A short delay of thirty to forty-eight hours, whilst all the steerage passengers are examined bacteriologically, as was practised at New York in the summer and autumn of 1911 (Krumwiede, 1911; Porter, 1911), is a serious logical attempt to cut the delay down to its shortest possible limit consistently with a bacteriological examination of each passenger. Even so short a delay means a serious interference with the movements of passengers, and may involve a considerable interference with trade. Besides these disadvantages, the occurrence of intermissions in excretion, as mentioned above, seriously detract from the value of such measures. At New York, between July 20 and November 16, 1911, 26,455 passengers were examined bacteriologically for cholera vibrios; 150 were detained for further examination, and 26 (1 per cent.) were eventually proved to be carriers.

It was found that the medical officer of health, with ten skilled assistants, could examine specimens from 1,000 cases in one day. On one day, 2,000 persons were examined at the port of New York.

In any case it is very necessary—

1. To isolate all cases of diarrhœa, however mild, in persons arriving from infected places, until bacteriological examination has excluded the presence of infective bacteria.

2. To keep up supervision over apparently healthy passengers arriving from infected places, and, in the event of suspicious symptoms occurring, either in recent arrivals or in other persons in his neighbourhood, to undertake bacteriological examination of the suspects.

Doty (1911) records the occurrence of a case of cholera imported from Italy into the United States.

The ship in which the person travelled came from Naples. No cases of cholera or diarrhœa had occurred on board, and only six passengers had been ill with some other complaints. The passengers, after landing, were supervised, and on the third day one passenger developed cholera and died. Cholera vibrios were isolated from his stools. It is therefore probable that unrecognized carriers were on board the ship throughout the voyage.

3. A search must be made for " carriers " in the surroundings of patients.

4. Patients and carriers must be carefully isolated until their stools give negative results on two or three occasions at intervals of about five days. It is probably an advantage, before releasing carriers from isolation, to administer a dose of magnesium sulphate and examine the resulting loose motion.

5. Discharged convalescents and carriers must be kept under observation and re-examined if cases occur in their neighbourhood.

6. Carriers must be instructed to wash their hands carefully before meals and after use of closets.

7. Disinfection of excreta, soiled linen, etc., and scrupulous attention to the cleanliness of closets, etc., must be enforced.

MacLaughlin (1911), during a prison epidemic, found that 6·3 per cent. of the apparently healthy prison inmates were carriers. When regulations as to washing of hands after the use of closets and before meals had been instituted, and were carefully carried out, no more cases of cholera occurred.

Regulations suited to the locality for preventing the spread of cholera must be drawn up on the following lines :

1. The cholera patients, convalescents, mild cases of diarrhœa in the neighbourhood of patients, and " healthy carriers " must be considered as potent sources of infection.

2. The supply of drinking-water must be regarded as possibly the immediate source of infection, especially if the water is liable to be contaminated by patients or carriers.

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INDEX

(D.), (Dys.), (C.), (M.), (T.), (P.), signify sections on Diphtheria, Dysentery, Cholera, Meningitis, Typhoid and Paratyphoid Fever respectively.

Abortive cases (D.), 192, 193
Abscesses of bone, *B. typhosus* in, 6, 8, 61, 149
Adenoids (D.), 218
Age of carriers (D.), 183, 206
Agglutination (C.), 298, 300
,, (Dys.), 274, 277
,, ,, by patient's serum, 278, 285
Agglutinins (Dys.), absorption of, 274 278
,, (P.), absorption of, 139, 140
,, (T.), in sera of carriers, 121-124
,, (Dys.), persistence of, 291
,, development of, in typhoid vaccination, 123, 124
Antitoxic sera (Dys.), 278, 281
Antitoxin (D.), 165, 172, 220
,, ,, from non-virulent *B. diphtheriae*, 194, 198
,, ,, in sera of carriers, 219
,, ,, in sera of patients, 194, 215
Aperients (C.), administration of, to carriers, 308
Army (T.), measures for dealing with carriers in, 128
Arsenic, administration of, in typhoid convalescence, 93
Asylum, cholera in, 305
Asylums (T.), bacteriological supervision of carriers in, 127
,, ,, carriers in, 51, 55
,, ,, isolation of carriers in, 127
Auto-infection (T.), in carriers, 78-82

B. coryzae segmentosus, 175 *et seq.*
B. diphtheriae, absence of, in communities, 187, 189
B. diphtheriae as cause of diphtheria, 165
,, characters of, 167
,, culture media for isolation of, 168, 171
,, dissemination of, 212
,, examination for, 168
,, identification of, 168, 170, 188
,, in lower animals, 201, 202
,, in scarlatina, 190, 191
,, isolation of, 171, 216, 224
,, non-virulent forms of, 176, 177, 193, 194, 199
,, non-virulent forms of, carriers of, 177, 189, 195 *et seq.*
,, non-virulent forms of, importance of, 193, 201, 215
,, non-virulent forms of, in contacts, 197, 200, 201
,, non-virulent forms of, in convalescents, 196, 197, 201-209
,, non-virulent forms of, in actual diphtheria cases, 197, 200
,, non-virulent forms of, in healthy persons, 200
,, non-virulent forms of, in non-contacts, 197
,, non-virulent forms of, occurrence of, 177, 192, 194 *et seq.*
,, occurrence of, in contacts, 181 *et seq.*, 186, 190, 192
,, occurrence of, in convalescents, 180, 193 *et seq.*, 200

B. diphtheriae, occurrence of, in diphtheria, 165, 180
,, occurrence of, in inanimate objects, 202
,, pathogenicity of, for animals, 172
,, persistence of, 203 *et seq.*, 209
,, variability of, 170
,, variations in virulence of, 193, 194
,, virulent and non-virulent forms of, 196, 199, 209
,, virulence of, in carriers, 193, 200
,, virulence of, in convalescents, 200, 201, 209
B. dysenteriae, abundance of, in fæces, 283, 288, 290
,, agglutination of, 271, 273
,, as cause of dysentery, 271, 280
,, carriers of, 286-291
,, characters of, 272
,, constancy of strains of, 275
,, culture media for isolation of, 276
,, dissemination of, 291
,, El Tor strains of, 271
,, Flexner strains of, 270
,, groups of, 272
,, in contacts, 280, 286
,, in convalescents, 282, 284, 287
,, indole-production by, 277
,, in healthy persons, 280, 283, 286
,, in mucus, 276, 282
,, in solid fæces, 276, 282
,, mannite - fermenting strains of, 272, 274, 275
,, mixed infections with Shiga and Flexner strains, 276
,, occurrence of, in the body, 281
,, occurrence of, in cases of dysentery, 280, 283
,, pathogenicity for animals of, 271, 273, 281
,, persistence of, 282 *et seq.*, 289, 290
,, Shiga strains of, 270, 273
,, toxicity of cultures of, 281
B. dysenteriae, toxin - production by, 273
,, variations of, 275
,, "Y" types of, 274, 277
B. enteritidis (Gaertner), carriers of, 155, 156
B. hofmanni, 173, 177, 212
B. maculatus, 176
B. paratyphosus B, formation of papillæ by, 141
B. pseudodiphtheriae, 164, 173
B. pseudodysenteriae, 271, 274, 275
B. septus, 175
B. suipestifer, cultural characters of, 138
,, carriers of, 154
,, habitat of, 137, 142, 143, 154, 155
,, pathological lesions in infections by, 155
B. typhosus, biochemical reactions of, 104, 105
,, detection of, by complement-fixation, 107
,, in blood of umbilical cord, 82
,, in fæces of rabbit carriers, 73
,, in relation to gall-stone formation, 67
,, non-motile forms of, 105
,, saprophytic existence of, 48
Bactericidal substances in sera of typhoid carriers, 59, 124
Bile, agglutinins in, 66
,, *B. typhosus* in, 62, 86, 87
Borovertin (T.) in treatment of urinary carriers, 98, 99, 101

Carbohydrate tests (D), 168, 176
,, ,, (Dys.), 273, 274, 277
Carriers (C.), chronic, 296, 307
,, ,, healthy, 304, 305, 306
,, ,, intermittent, 308
,, (D.), absence of, 216
,, ,, age of, 181
,, ,, catarrhal symptoms in, 213
,, ,, chronic, 166, 209
,, ,, classification of, 166, 183
,, ,, convalescent, 180, 183
,, ,, detection of, 213, 223
,, ,, early observations with regard to, 163, 164
,, ,, efficient, 214, 217
,, ,, frequency of, 183 *et seq.*, 213, 192
,, ,, healthy, 181, 183, 184, 186, 188, 189, 190, 192, 219

Carriers (D.), infectivity of, 185, 211
,, ,, in schools, 184
,, ,, intermittent, 208
,, ,, isolation of, 185, 186, 223
,, ,, nasal, 192, 214
,, ,, precocious, 191
,, ,, temporary, 209
,, (Dys.), chronic, 288, 289, 290
,, ,, convalescent, 287, 289
,, ,, healthy, 286, 290
,, ,, precocious, 287
,, ,, relapsing, 285, 288
,, (M.), agglutinins in sera of, 257, 261-264
,, ,, auto-infection in, 258
,, ,, in families, 241, 242, 244, 249
,, ,, persistence in throats of, 252
,, (T.), army, 57-61
,, ,, auto-infection in, 63
,, ,, chronic, definition of, 12
,, ,, chronic urinary, 6
,, ,, distinction between temporary and chronic, 76
,, ,, female, preponderance of, 23, 24, 67, 74
,, ,, gall-stone disease in, 67
,, ,, general statistics of, 23-30
,, ,, in general population, 21, 22
,, ,, in neighbourhood of patients, 19
,, ,, institutional, 51-57
,, ,, intermediate, 49
,, ,, intestinal, treatment of, 82-93
,, ,, sex of, 24
,, ,, symptomless, 18, 48
,, ,, temporary, 48, 49, 93
,, ,, urinary, infectivity of, 35, 36, 57-61
,, ,, urinary, treatment of, 97-101
Carrier-state (M.), pathogenesis of, 253-260
,, (T.), experimental production of, 72-74
Chemotherapy (T.), 83
Chloroform (T.), use of, in experimental rabbit carriers, 84
,, ,, use of, in human carriers, 84
Cholecystectomy (T.), development of enteric fever after, 81
Cholecystitis (T.), 61, 63, 65
Cholelithiasis (T.), 8, 61
Child-birth (T.), infectivity of carriers at, 39
,, ,, relaxation of hygienic precautions at, 39
Cholera, 295 *et seq.*
,, diagnosis of, 297
,, isolation in, 310
,, slight symptoms in, 304
Cholera vibrio, agglutination of, 298, 300, 301
,, ,, characters of, 297 *et seq.*
,, ,, culture media for isolation of, 299
,, ,, detection of, 297, 298, 309
,, ,, detection of, by complement-fixation, 298, 302
,, ,, El Tor strains of, 302
,, ,, occurrence of, in body, 296, 304
,, ,, occurrence of, in convalescents, 304, 308
,, ,, occurrence of, in cases of cholera, 295, 300
,, ,, occurrence of, in gall-bladder, 304, 307
,, ,, pathogenicity of, 299
,, ,, persistence of, 295, 304 *et seq.*
,, ,, toxicity of, 299
,, ,, variations of, 300
,, ,, viability of, 303
,, ,, virulence of, 299
Cholera-like vibrios, 301, 302
Cold (Dys.), effect of, on carriers, 290
Colitis (Dys.), ulcerative, 279, 285
Complement-fixing substances (T.) in sera of carriers, 125
Conjunctivitis (D.), 178, 179
,, (Dys.), 282
Convalescent homes (T.) for recovered typhoid cases, 126
Cures (T.), so-called bacteriological, 82
Cystitis (T). in urinary carriers, 95
Cystoscopy (T.) in urinary carriers, 95

Depots (T.), bacillary, in gall-bladder, 72, 73, 74, 90
Diarrhœa (C.), mild, 295, 311
,, (Dys.), catarrhal, 280, 282
,, ,, summer, 279
Diphtheria, 163-226
,, (D.), chronic, 210
,, ,, diagnosis of, 170
,, ,, in the guinea-pig, 165, 172
,, ,, of skin, 178 *et seq.*
,, ,, post-operative, 192

Diphtheroid bacilli, 167, 169, 173 *et seq.*
Disinfectants (T.) for the hands of carriers, 131
Disinfection (D.), 224
Dose (T.), magnitude of, 108
Dysentery, 270-294
,, (Dys.), asylum, 272, 279, 280
,, ,, chronic, 282, 285, 288
,, ,, grographical distribution of, 272, 279
,, ,, infectivity of, 291
,, ,, isolation of cases of, 284, 287
,, ,, mild forms of, 271, 280, 282, 290
,, ,, in monkeys, 281, 293
,, ,, relapsing, 285, 288
,, ,, sporadic, 271, 274, 279, 285
,, ,, spread by contact, 290, 292

Ear (D.), infection of, 170, 175, 177, 178, 205, 211, 214
Eczema (D.), 179, 180
Endemics (T.) in country districts, 34, 35, 36
,, ,, in households, 30, 31, 32, 33, 35
Excreta (T.), disinfection of, 5, 34
Excretion of typhoid bacilli, spontaneous cessation of, 26

Fæces (T.), daily examination of, 16, 17
,, ,, examination of, in convalescence, 9, 11, 13, 14
,, ,, examination of, in the course of enteric fever, 9, 10
,, ,, examination of, in incubation period, 11, 28, 29
,, ,, isolation of *B. typhosus* from, 104, 105
,, ,, late control examination of, 14, 15
, ,, late control examination of, advantages of, 15
Fœtus (T.), infection of, in pregnant carriers, 81, 114
Foodstuffs (Dys.) as vehicles of infection, 292
,, (T.) as vehicles of infection, 33, 50, 128, 131

Gaertner - paratyphoid group, distribution of, in man and animals and foodstuffs, 140-146
Gall-bladder (C.), infection of, 304, 307
,, (T.), infection of, 3, 24, 27, 62
,, ,, bacillary depots in, 64
,, ,, removal of, 87, 88, 89, 90
,, infection (T.), pathogenesis of, 73
Gall-stones (T.), *B. typhosus* in, 62, 65, 68, 80
,, ,, experimental production of, 70
,, ,, in fæces, 68
,, ,, penetration of, by *B. typhosus*, 71
,, ,, rapid formation of, 70
,, ,, sterility of, 70
,, ,, viability of *B. typhosus* in, 69
Genito-urinary system, chronic typhoidal infection of, 3, 93-97
Glucose (D.), fermentation of, 168, 173

Hæmotoxin (C.), production of, by vibrios, 299
Hetralin (T.), administration of, in urinary carriers, 98
Home (D.) as source of infection, 185, 187, 218
Houses (D.) associated with diphtheria, 216

Immunity reactions (D.), 212, 215
,, ,, ,, in carriers, 219
,, ,, (T.). in carriers, 121-125
Immunity phenomenon (T.), carrier-state as, 40, 41
Incubation stage (T.), infectivity of patients during, 27-30
Infection, chronic typhoid, 3
,, nature of, 2
,, (D.), sources of, 185, 187
,, (T.), marital, in carriers, 40, 41
Infections (T.), contact, 28, 29, 30
Infectivity (D.) of carriers, 179, 185, 211, 217
,, (Dys.), 291
,, (T.), general question of, 108-115
,, ,, of carriers, statistical data of, 115-121
,, ,, seasonal, 115
Institutions (D.), outbreaks in, 184
,, (T.), outbreaks in, 51-57
Instructions (T.) for control of carriers, 128, 129, 130
Insusceptibility (D.), 212
Intermittency (C.) in excretion of bacilli, 308

Intermittency (D.) in excretion of bacilli, 208
,, (Dys.) in excretion of bacilli, 287
,, (T.) in excretion of bacilli, 15, 83, 108
Isolation (C.) of carriers, 310
,, (D.) of carriers, 185 *et seq.*, 208, 225
,, (Dys.) of carriers, 284
,, (M.) of carriers, 266, 267

Kidney (T.), calculi of, 100
,, ,, lymphomata in, 97
Kidney-pelvis (T.), disease of, 94, 97

Lactobacillin (T.), use of, in treatment, 85
Laryngitis (D.) in carriers, 178, 211
Legislative measures (T.) for control of carriers, 131
Local immunity theory (T.), 125
Lymphatism (M.), 253, 254, 255

Mannite (Dys.), fermentation of, 273
Media (T.) for isolation of *B. typhosus*, 106, 107
Meningitis, cerebrospinal, first appearance of, 227
,, cerebrospinal, hæmophilic organisms in, 261
,, cerebrospinal, in America, 227
,, cerebrospinal, in Great Britain, 228-231
,, cerebrospinal, in India, 228
,, cerebrospinal, in military barracks, 232
,, cerebrospinal, in tropical countries, 228, 233
,, cerebrospinal, in young children, 233, 234
,, cerebrospinal, limitation to certain classes, 232
,, cerebrospinal, main features of, 231-234
,, cerebrospinal, mortality from, 234
,, cerebrospinal, post-basic, 261
,, cerebrospinal, seasonal incidence of, 232, 233
Meningococcal carriers, agglutinins in sera of, 261-263
,, carriers, bactericidal substances in sera of, 262
,, carriers in military barracks, 245, 246, 248
Meningococcal carriers, opsonic substances in sera of, 263
,, carriers, pharyngitis in, 245, 246
,, carriers, treatment of, 264, 266
Meningococcus, discovery of, 234
,, extra-corporeal vitality of, 238
,, healthy carriers of, 240-252
,, in patients and carriers, 237-252
,, isolation and identification of, 235, 236
Meningococcus, period of survival of, in convalescents, 239, 240
Mice (P.) as carriers of Gaertner-like organisms, 143
Milk (D.), transference of infection by, 202, 224
,, (T.), transference of infection by, 41-50
,, ,, treatment by sour, 84, 85
,, ,, as diet in convalescence, 92
Milk-borne outbreaks (T.), age incidence of affected in, 46
Mining districts, cerebrospinal fever in, 259
Monkeys, dysentery in, 281

Nasal carriers (D.), 178, 214
,, discharge (D.), 184, 192, 217
Naso-pharynx (M.), examination of, 235
,, ,, examination of, in cases of meningitis, 237 - 239, 253
,, ,, examination of, in healthy children, 254, 256
Neisser's granules (D.), 170, 173, 176, 198
Nephrectomy (T.) in urinary carriers, 96
Nose (D.), bacilli in, 176, 177, 178, 190, 193
Notification (M.) of carriers, 267
Nurses (D.), infection of, 185, 187, 211

Operations (D.), surgical, in carriers, 191, 221
Opsonins (D), 219
,, (T.), 125
Otorrhœa (D.), 177, 211

Paratyphoid bacilli in bone abscesses, 149
,, ,, in gall-bladder, 148-150

Paratyphoid bacilli in prostatic secretion, 150
,, ,, in urine, 150
,, ,, isolation of, 139
,, carriers, auto-infection in, 150, 151
,, ,, frequency of, 147
,, ,, instances of infectivity of, 151-154
,, A carriers, acute, 160
,, ,, infectivity of, 160, 161
,, fever, clinical symptoms of, 137
,, ,, frequency of, 136
,, ,, gall-bladder complications in, 148-151
,, ,, pulmonary complications in, 150
,, A fever, clinical features of, 157, 158
,, ,, gall-bladder complications in, 159
,, ,, occurrence in India, 156-161
Paratyphoid-like organisms in canaries, 142
,, organisms in cattle and horses, 142
,, organisms in flies, 142
,, organisms in foodstuffs, 143
,, organisms in guinea-pigs, 142
,, organisms in man, 144-146
,, organisms in swine, 142
Pettenkofer (T.), thesis of, 3
Pfeiffer's reaction (C.), 299
Pharyngitis, meningococcal, 256-258
Pneumonia (T.), typhoid bacilli in blood of cases of, 112
Pregnancy (T.) as predisposing factor, 113
Public health measures (C.), 309
,, ,, ,, (D.), 222
,, ,, ,, (Dys.), 293
,, ,, ,, (M.), 264-267
,, ,, ,, (T.), 126-131
Puerperal state (T.) as predisposing factor, 113, 114
Pyonephrosis, typhoidal, 96

Quarantine (C.), 309

Reinfection (T.), symptomless, 41, 75
Return cases (D.), 214
Rhinitis (D.), atrophic, 210, 219
,, ,, membranous, 178, 210, 219

Saliva (D.), bacilli in, 177, 213
Saprophyte, *B. typhosus* as, 56
Scarlet fever (D.), 190, 191, 196
School (D.) as source of infection, 183, 185, 187
Septicæmia, meningococcal, 259, 260
Serological methods (T.) in diagnosis, 105
Serum (Dys.), therapeutic, 271, 278, 281
Skin (D.), infection of, 178 *et seq.*
Soil, prolonged sojourn of organisms in, 3
Sore throat (D.), slight, 166, 182, 183, 186, 192, 193, 214
Staphylococci (D.), treatment by live, 221
Stations (T.), bacteriological, 5, 7
,, ,, bacteriological, functions of, 7
Statistics (T.) of carrier infectivity, 120
Stomach contents (T.), isolation of *B. typhosus* from, 106
Surgical treatment (T.) of carriers, 85-91

Tonsils (D.), enlargement of, 184, 192, 218
Trauma (T.) as predisposing factor, 113
,, (M.,) as predisposing factor, 259, 267
Treatment (D.) of carriers, 220 *et seq.*
,, (Dys.) of carriers, 293
,, (T.) of carriers, 82-93, 97-101
,, (M.) of carriers, 264-265
Tropins (T.) in sera of carriers, 125
Tuberculous patients (T.), typhoid bacilli in blood of, 111, 112
Typhoid fever, abortive cases of, 5, 8, 20
,, ,, ambulant cases of, 5, 8, 20
,, ,, atypical cases of, 8, 20, 56
,, ,, clinical symptoms of, 20

Ubiquity of diphtheria bacilli, 164
,, of "paratyphoid" bacilli, 145
Ulcers (Dys.), chronic, 282
Urethra (D.), bacilli in, 175
Urine (D.), bacilli in, 180
Urotropin (T.) in treatment, 97, 98

Vaccine-therapy (D.) in treatment, 220
,, (T.) in treatment, 91
Vagina (D.), bacilli in, 178
Vibrios (C.), non-pathogenic, 301
Virulence (D.) of strains for animals, 172, 185, 193, 194, 215, 224
,, (T.) of strains for animals, 109, 110
,, (D.), method of testing, 171, 225
,, (T.), method of testing, 109, 110
Virulence (T.), periodical test of, 110

Water-supply (C.) as source of infection, 296, 303, 309, 311
,, (Dys.) as source of infection, 292
Whitlows (D.) in carriers, 179
Widal reaction (T.) in diagnosis, 101, 102, 103
,, ,, ,, in tuberculosis, 113

X rays (T.), treatment by, 91

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